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INTERVENTIONAL

Ultrasound-guided transthoracic needle biopsy of the lung: sensitivity and safety variables

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Abstract

Objectives Variables affecting the performance of ultrasound-guided transthoracic needle biopsy (US-TTNB) are not well established. We examined clinical and imaging variables affecting the sensitivity and the complication rates of US-TTNB.

Methods We retrospectively reviewed a consecutive series of 528 US-TTNBs performed from 2008 to 2017. Univariate analyses were used to assess the influence of clinical and imaging variables on sensitivity and complication rates. Multivariate logistic regression was used to account for possible confounding variables.

Results In 397 malignant lesions, the sensitivity of US-TTNB was 72% (95% CI 68–77%; 285/397). The overall pneumothorax rate was 15% (95% CI 12–18%; 77/528), leading to a chest tube in 2% (95% CI 1–3%; 9/528). Multivariate analysis showed that increasing pleural contact length (up to 30 mm) was associated with increased sensitivity (OR 1.08 per mm; 95% CI 1.04–1.12; $p < 0.001$), and pleural contact length (OR 0.98 per mm; 95% CI 0.97–0.99; $p = 0.013$), lesion size (OR 0.98 per mm; 95% CI 0.96–0.99; $p = 0.006$), and core needle diameter of 18G (OR 0.47 as compared with 20G; 95% CI 0.26–0.83; $p = 0.010$) were associated with a decreased pneumothorax rate. Graphical inspection of cubic splines showed that the probability of a positive biopsy rose sharply with increasing pleural contact length up to 30 mm and was stable thereafter. A similar, but inverse, relationship was observed for the probability of a pneumothorax.

Conclusion Pleural contact length is a key variable predicting the sensitivity of US-TTNB and pneumothorax rate after US-TTNB. Lesion size also predicts pneumothorax rates.

Key Points

- *US-TTNB has a high sensitivity and a low complication rate for pleural and pulmonary lesions with pleural contact.*
- *Pleural contact length is a key variable predicting the sensitivity of US-TTNB and pneumothorax rate after US-TTNB.*
- *This study suggests that relying on US-TTNB may not be optimal for lesions < 10 mm for which the risk of pneumothorax is as high as the chance of obtaining diagnosis.*

Keywords Biopsy, needle · Lung · Ultrasonography, interventional · Lung neoplasms

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Abbreviations

95% CI	95% confidence interval
CT	Computed tomography
CT-TTNB	Computed tomography-guided transthoracic needle biopsy
FEV1	Forced expiratory volume in 1 s
FNA	Fine-needle aspiration
IQR	Interquartile range
OR	Odds ratio
PET	Positron emission tomography
PGY	Post-graduate year
TTNB	Transthoracic needle biopsy
US	Ultrasound
US-TTNB	Ultrasound-guided transthoracic needle biopsy

Introduction

Transthoracic needle biopsy (TTNB) is a common and minimally invasive procedure to obtain a tissue diagnosis in patients with lung lesions [1]. Imaging guidance to direct the biopsy needle has been integral to the evolution of TTNB. As imaging technology evolved, so did the type of guidance used: fluoroscopy gave way to ultrasound (US) and computed tomography (CT), and new technologies paved the way for C-arm cone-beam CT and electromagnetic navigation systems [2–4]. CT-guided TTNB (CT-TTNB) is recommended as the primary modality for thoracic image-guided biopsy in international guidelines as it currently offers the best spatial resolution [5], despite being time-consuming especially for small peripheral pulmonary lesions, and carrying the risk of radiation exposure [6]. Conversely, US guidance is routinely the method of choice to biopsy anterior mediastinal and chest wall lesions, especially since recent technological advances in transducer design and signal processing have greatly improved the quality of US imaging [6–8]. Moreover, US guidance increases patient accessibility to TTNB and offers advantages including continuous real-time imaging capabilities, the ability to obtain tissue during a single breath, the absence of ionizing radiation, and a short duration of the procedure [6, 9–11].

Although the diagnostic accuracy and complication rates of US-TTNB have been evaluated in a few studies [2, 12, 13], the impact of clinical and imaging variables on sensitivity and complications remains largely unknown [14]. In contrast, variables affecting CT-guided TTNB have been thoroughly examined in large cohorts [15–18]. The aim of this study was to identify clinical and imaging variables affecting the sensitivity and complication rates of US-TTNB for diagnosing pulmonary lesions using a large cohort of consecutive biopsies from a single institution.

Material and methods

The manuscript was drafted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19].

Patients

We retrospectively reviewed all TTNB performed by our institution's radiology department between January 1, 2008, and December 31, 2017. Exclusion criteria were CT guidance, lesions that originated from the mediastinum or chest wall, records with incomplete data, and the inability to visualize the lesion with ultrasound (Fig. 1). The study was approved by the Institutional Review Board (#2018-3032, 21593), and the requirement for patient consent was waived due to the retrospective nature of the analysis.

Procedure

All requests for TTNB were reviewed by a radiologist according to a local practice algorithm. Guidance method (CT versus US) was based on the target lesion's axial imaging characteristics (Supplemental Data: Supplemental Figure 1, which shows our decision-making algorithm). US guidance was attempted for lesions with pleural contact ≥ 10 mm and a solid component; CT guidance was used for all other lesions. Clopidogrel and acetylsalicylic acid were stopped for ≥ 5 days, and low molecular weight heparin was withheld for one dose prior to the procedure to ensure an international normalized ratio (INR) < 1.5 and a platelet count > 50,000/μl, according to contemporary recommendations [20].

US-TTNBs were performed using a curvilinear or straight linear array ultrasound with either a Philips ATI HDI 5000 (2008) or a Toshiba Aplio XG (2009 to 2017) ultrasound machine. Patients were placed in the supine, prone, or lateral decubitus position to yield the easiest access for the desired acoustic window. The needle was inserted through the skin directly into the plane of view of the transducer using a free-hand approach without a guide [6]. During the procedure, patients breathed spontaneously and were instructed to hold their breath, if needed, while the biopsy was being performed. Core biopsy was the preferred sampling tool, but fine needle aspiration (FNA) was used when dictated by anatomical constraints. The use of both core biopsy and FNA occurred when the primary passage, most often with a co-axial needle, gave the assurance of using both biopsy tools. Lesions sampled by FNA were always biopsied with a 20G needle. In contrast, core biopsies were most often completed using an 18G needle.

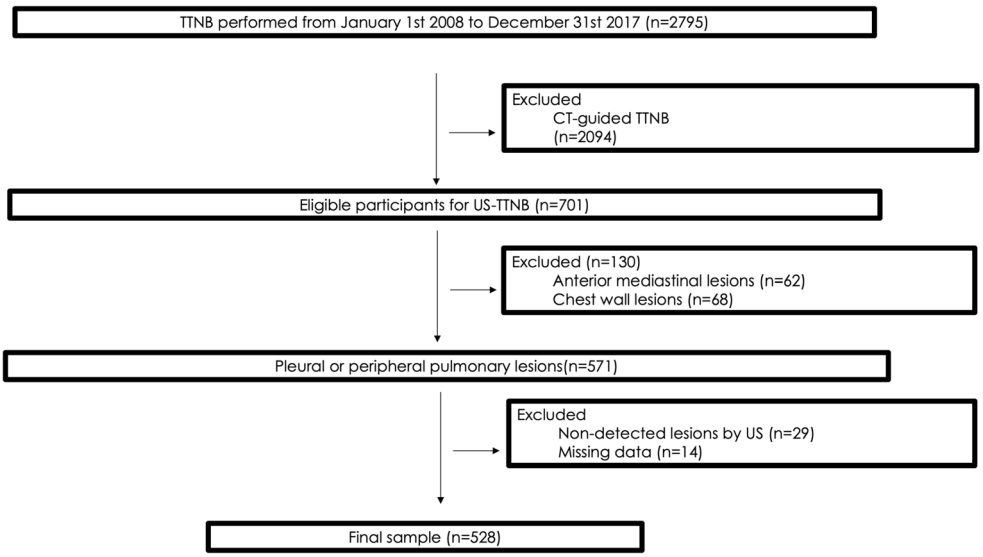

Fig. 1 Study flowchart. Flowchart of patients who underwent TTNB with exclusion criteria for the current study noted. TTNB, transthoracic needle biopsy; CT, computed tomography; US, ultrasound

Assessment of post-TTNB pneumothorax was systematically performed immediately after the procedure using the US probe [21] and with chest radiographs obtained 1 and 3 h after the procedure. A thoracic pathologist analyzed the biopsy specimens; a cytopathologist was not on site during the procedure.

Data collection

Medical records were queried for age, sex, prior intrathoracic surgery, and forced expiratory volume in 1 s (FEV1). All pre-TTNB imaging (CT/PET-CT) was reviewed by a PGY-2 radiology resident (S.L.), without knowledge of the corresponding US-TTNB pathology report. The resident assessed pulmonary emphysema and fibrosis (visually assessed and classified as none, mild, moderate, or severe), pleural or pulmonary origin of the lesion, pleural contact length, lesion size (longest diameter), lobar anatomy, circumferential anatomy (Supplemental Data: Supplemental Figure 2, which shows classification of lesion location), lesion composition, anatomical contact (diaphragm/vertebra/apical location), and chest wall invasion. Procedure variables assessed were needle type, needle diameter, radiologist's experience, medical resident involvement, number of transthoracic passages, complications, the need for chest tube drainage, and the duration of chest tube drainage. Repeat US-TTNBs performed in the same patient, but on a different lesion or a progressed lesion that presented with interval growth on axial imaging after a prior non-diagnostic US-TTNB, were considered separate procedures.

Outcomes and reference standard

Our efficacy outcome was sensitivity, defined as the true positive rate. A TTNB was classified as diagnostic if the original pathology report provided a malignant diagnosis or a specific benign diagnosis (e.g., tuberculoma). A TTNB that provided non-specific benign pathological findings, atypical cells, or an insufficient specimen was classified as non-diagnostic, even if the final diagnosis of the lesion was benign [22]. We constructed 2 × 2 tables according to original pathology reports classifying the TTNBs as true positives (malignant diagnosis), true negatives (specific benign diagnosis), false positives (falsely malignant diagnosis), and false negatives (non-specific benign, atypical cells and insufficient specimen pathological findings). The negative predictive value was also calculated.

Final diagnoses of malignancy and benignity of the target lesions were determined according to a reference standard determined a priori [22, 23]. When available, the final diagnosis was made from the pathology report from a surgical resection or autopsy. If the pathology report from a US-TTNB, CT-TTNB, or transbronchial biopsy showed a malignant or a specific benign diagnosis, the pathological finding was accepted as the final diagnosis. For other lesions, a final diagnosis of benignity was attributed when appropriate clinical and radiological follow-up showed stability over 2 years or regression of at least 20% or disappearance without oncologic treatment. The lesion was considered malignant when the clinical course was consistent with obvious malignant processes. Lesions that did not fulfill any of the criteria detailed above were classified as indeterminate and excluded from the analysis. When the pathology report from a US-TTNB was used as the final diagnosis, an additional medical record search was performed to retrieve available surgery or autopsy reports of the lesion to screen for false positives.

We examined complication rates as a safety outcome. Complications examined included pneumothorax,

hemorrhagic complications, and severe complications such as death, massive hemothorax, or air embolism.

Statistical analysis

Data are presented as mean ± standard deviation or median (interquartile range [IQR]). Continuous variables were compared using Student's T-test, and categorical variables were compared using chi-square test. Univariate analyses were performed to assess the influence of clinical and imaging variables on sensitivity (n = 397) and complication rates (n = 528). When needle size was examined, only the core biopsies were included in the analysis to minimize confounding by different procedure types. Variables with $p < 0.05$ in the univariate analysis were included in multivariate logistic regression models. Variables of interest for sensitivity and complications were pleural contact length, lesion size, core needle diameter, chest wall invasion, the occurrence of pneumothorax, radiologist experience, medical resident involvement, number of transthoracic passages, diaphragmatic contact, and apical location. Emphysema on imaging and FEV1 was also assessed relative to pneumothorax rates. Cubic splines with 95% CI were used to graphically examine the functional relationship of sensitivity and pneumothorax rate with pleural contact length. Analyses were done with SAS 9.4 (SAS Institute Inc.).

Results

Patient demographics and lesion characteristics

Between 2008 and 2017, 2795 consecutive TTNBs were performed with either CT or US guidance. After exclusion criteria were applied, the study population comprised 488 patients who had undergone a consecutive series of 528 US-TTNBs (Fig. 1). The mean age of the 286 men and 242 women who underwent US-TTNB was 68 ± 11 years (Table 1). Prior to the US-TTNB, 20% of the patients (107/528) had at least 1 ipsilateral intra-thoracic surgery. A final diagnosis of malignancy was made in 397 lesions (75%). Most lesions were considered of pulmonary origin (91%; 479/528) rather than pleural origin (9%; 49/528). Biopsied lesions were in contact with the diaphragm in 19% of patients (98/528), abutted a vertebra in 22% (115/528), and were in an apical location in 30% (161/528). Median pleural contact length was 32 mm (IQR 18–61; range 8–231) and median lesion size was 35 mm (IQR 20–55; range 6–153; Table 2; Supplemental Data, Supplemental Figure 3, which shows distribution of lesion pleural contact length and size).

Sensitivity and diagnostic accuracy

US-TTNB was performed by one of 20 radiologists with average 8 ± 7 years of experience (Table 2). Radiology residents participated in 55% of the procedures (288/528) under the supervision of the radiologist. The non-detection rate for lesions by ultrasound was 5% (95% CI 3–7%; 29/571) and was caused by the interposition of the scapula or of ribs between the lesion and the ultrasound transducer. When a lesion could not be detected by US, the patient was rescheduled for a CT-TTNB on the same day.

Core biopsy was the preferred sampling tool (67%; 353/528); FNA was used in 21% of patients (113/528), and core biopsy and FNA were used together in 12% of patients (62/528). Lesions sampled by FNA were always biopsied with a 20G needle. Core biopsies were most often completed using an 18G needle (55%, 229/415, vs 38%, 159/415 with a 20G needle). US-TTNB was completed with one transthoracic passage in 52% of patients (273/528). A co-axial technique was used in only 5% of biopsies (24/528) (Table 2).

The sensitivity of US-TTNB for malignancy in our study population was 72% (95% CI 68–77; 285/397), whereas the negative predictive value was 54% (95% CI 50–58; 131/243). Overall diagnostic accuracy, defined as the rate of true positives and true negatives, was 59% (95% CI 54–62; 312/528). Surgical or autopsy pathology reports were available in 92 patients diagnosed using US-TTNB and did not reveal any false positives for a specificity of 100% (92/92) (Supplemental Data: Supplemental Figure 4A, which shows distribution of outcomes).

In a univariate analysis, sensitivity was associated with pleural contact length, lesion size, chest wall invasion, and the use of an 18G core needle, whereas the occurrence of pneumothorax was associated with lower sensitivity (Table 3). Other variables defined a priori did not influence the sensitivity of the procedure. Only pleural contact up to 30 mm (OR 1.08 per mm; 95% CI 1.04–1.12; $p < 0.001$) remained associated with the procedure's sensitivity in a multivariate analysis. After the pleural contact length exceeded 30 mm, further increases in pleural contact length had no effect on sensitivity.

Because we found that pleural contact length was strongly associated with sensitivity in our multivariate analyses, we modeled this association using a cubic spline. Graphical inspection of the cubic spline showed that the sensitivity rose sharply for increasing pleural contact length up to 30 mm (Fig. 2a).

Complications

Pneumothorax occurred as a result of 77 US-TTNB procedures (15%; 95% CI 12–18) and led to a chest tube in 9 patients (2%; 95% CI 1–3%) (Supplemental Data:

Table 1 Patient demographics and lesion characteristics

	Total $n = 528$*	Diagnostic success $n = 312$ (59%)	Diagnostic failure $n = 216$ (41%)	p value
Age, year[1]	68 ± 11	69 ± 11	67 ± 10	0.073
Sex, n (%)				0.738
Male	286 (54)	171	115	
Female	242 (46)	141	101	
Fibrosis, n (%)	40 (8)	26	14	0.423
Emphysema, n (%)	176 (33)	101	75	0.573
Prior ipsilateral intrathoracic surgery, n (%)	107 (20)	64	42	0.729
Final diagnosis, n (%)				< 0.001
Adenocarcinoma	163 (31)	108	55	
Squamous cell	99 (19)	84	15	
Other	135 (26)	93	42	
Benign	131 (25)	27	104	
Pleural contact length (mm), median (IQR)	32 (18–61)	37 (20–69)	26 (15–52)	0.013
Size (mm), median (IQR)	35 (20–55)	38 (22–60)	28 (18–46)	< 0.001
Pleural origin, n (%)				0.119
Pulmonary	479 (91)	278	201	
Pleural	49 (9)	34	15	
Lobar anatomy, n (%)				0.091
Upper lobe	268 (51)	170	98	
Middle and lower lobe	260 (49)	144	116	
Circumferential anatomy, n (%)				0.131
Anterior	101 (19)	64	37	
Lateral	96 (18)	46	50	
Posterior	224 (42)	135	89	
Anterolateral	33 (6)	23	10	
Posterolateral	44 (8)	24	20	
Circumferential	30 (6)	20	10	
Composition, n (%)				0.174
Solely solid	426 (81)	247	179	
With ground-glass opacity	24 (5)	15	9	
Cavitary or with necrosis	79 (15)	50	28	
Contact, n (%)				
Diaphragm	98 (19)	51	46	0.139
Vertebra	115 (22)	66	48	0.141
Apical location	161 (30)	107	54	0.026
Chest wall invasion, n (%)	34 (6)	30	4	< 0.001

IQR, interquartile range

[1] Presented as mean ± standard deviation

*488 patients with 40 repeat TTNBs, which were analyzed as separate procedures, due to the biopsy of a different site/lesion

Supplemental Figure 4A, which shows the distribution of outcomes). Median duration of chest tube drainage was 1 day (range 1–6). A univariate analysis revealed that pneumothorax rates were inversely correlated with pleural contact length and lesion size and were less frequent during US-TTNB biopsy of lesions with an apical location or when an 18G core needle was used (Table 4). Two models were built for multivariate analysis, one that excluded lesion size and one that excluded pleural contact length, given the high collinearity between these 2 variables (Supplemental Data: Supplemental Figure 5, which shows collinearity). Increasing pleural contact length (OR 0.98 per mm; 95% CI 0.97–0.99; $p = 0.013$), increasing lesion size (OR 0.98 per mm; 95% CI 0.96–0.99;

Table 2 Procedure characteristics

	Total of US-TTNB $n = 528$
Number of radiologists, n	20
Radiologists' experience, mean in years ± SD	8 ± 7 (range 0–32)
Participation of a radiology resident, n (%)	288 (55)
Number of transthoracic passages, n (%)	
1	273 (52)
2	190 (36)
3	46 (9)
≥ 4	19 (4)
Biopsy tool type	
Core biopsy	353 (67)
Fine needle aspiration	113 (21)
Both	62 (12)
Needle size[1], n (%)	
Core biopsy – 20G	229 (43)
Core biopsy – 18G	159 (30)
Core biopsy – other	27 (5)
Fine needle aspiration – 20G	113 (21)
Co-axial technique, n (%)	24 (5)
Complications, n (%)	
Pneumothorax	77 (15)
Pneumothorax requiring chest tube[2]	9 (2)
Parenchymal hemorrhage	12 (2)
Hemoptysis	5 (1)
Duration of chest tube drainage, median in days	1 (range 1–6)

SD, standard deviation; *US-TTNB*, ultrasound-guided transthoracic needle biopsy

[1] Needle size corresponds to the largest needle size inserted during a single US-TTNB procedure

[2] The 9 patients who needed chest tube drainage are included in the 77 patients with pneumothoraxes

$p = 0.006$), and the use of an 18G core needle were associated with lower pneumothorax rates.

Analysis of a cubic spline demonstrated that the likelihood of a pneumothorax decreased steadily with increasing pleural contact length (Fig. 2b). Consistently, the ratio of sensitivity over the probability of pneumothorax proportionally increased with pleural contact length (Fig. 2c), indicating that as the lesion to be biopsied had more contact with the pleura, the likelihood of a diagnosis using US-TTNB increased and the likelihood of pneumothorax as a complication of the procedure decreased.

Hemorrhagic complications occurred in 17 of the procedures (3%, 95% CI 2–5%), including parenchymal hemorrhage in 2% (95% CI 1–4%) and hemoptysis in 1% (95% CI 0–2%). None of the variables that we defined influenced the occurrence of hemorrhagic complications. No severe complication occurred in our cohort.

Discussion

In this retrospective study of variables affecting the performance of US-TTNB, increasing pleural contact length was associated with higher sensitivity and a lower pneumothorax rate. Lesion size and core needle diameter of 18G were also associated with a lower pneumothorax rate. Conversely, hemorrhagic complications were rare and not influenced by any of the variables we analyzed. The present study is by far one of the largest cohorts of consecutive US-TTNB examined to date. Our study established a linear relationship between sensitivity, pneumothorax rate, and pleural contact length during US-TTNB. More importantly, the study allowed us to identify variables that influence the sensitivity and complication rates of US-TTNB that are readily accessible in day-to-day clinical

Table 3 Variables affecting sensitivity

Variable	Univariate Odds ratio (95% CI)	*p* value	Multivariate Odds ratio (95% CI)	*p* value
Pleural contact length, per mm	1.01 (1.00–1.02)	0.007	1.08 (1.04–1.12) [up to 30 mm]	< 0.001
			1.00 (0.99–1.00) [30 mm and higher]	0.320
Lesion size, per mm	1.02 (1.01–1.03)	< 0.001	1.01 (0.99–1.03)	0.280
Chest wall invasion	5.73 (1.33–24.6)	0.019	3.79 (0.85–16.9)	0.081
Needle size (core), 18G vs 20G	1.75 (1.08–2.94)	0.025	1.56 (0.91–2.70)	0.104
Occurrence of pneumothorax	0.40 (0.21–0.74)	0.003	0.83 (0.37–1.83)	0.630
Pneumothorax with chest tube	0.20 (0.05–0.86)	0.031	0.20 (0.03–1.21)	0.081
Diaphragmatic contact	1.26 (0.69–2.33)	0.450		
Apical location	1.52 (0.94–2.46)	0.090		
Radiologist experience, per year	1.00 (1.00–1.00)	0.089		
Number of transthoracic passages	1.12 (0.84–1.50)	0.450		
Medical resident involvement	1.24 (0.80–1.92)	0.090		

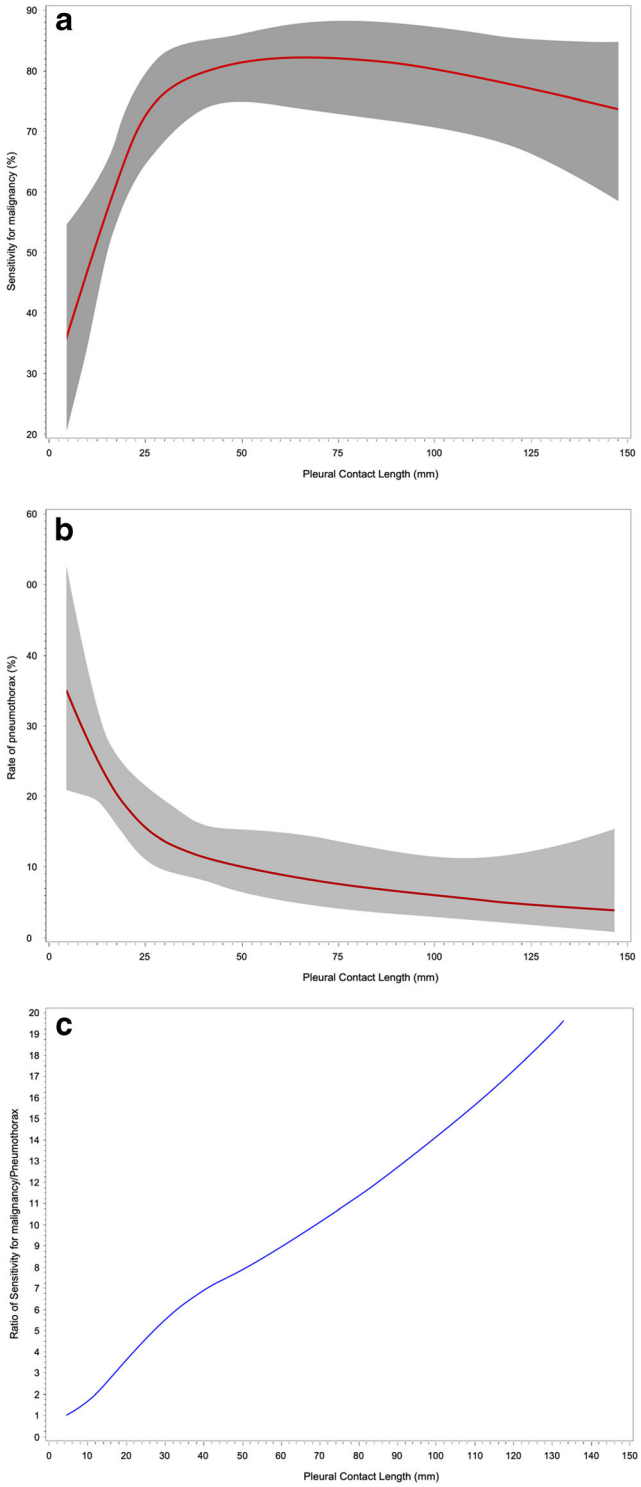

Fig. 2 Functional relationship of sensitivity for malignant lesions and pneumothorax rate according to pleural contact length. Cubic splines demonstrate (**a**) the linear relationship (red line) of sensitivity and pleural contact length with 95% confidence interval (shaded gray area); (**b**) linear relationship (red line) of the pneumothorax rate and pleural contact length with 95% confidence interval (shaded gray area); (**c**) the linear ratio of the sensitivity over the probability of pneumothorax according to the pleural contact length

practice and can assist physicians in making objective decisions about the best diagnostic procedure for patients with thoracic lesions with pleural contact. Indeed, our results suggest that radiologists should assess pleural contact length prior to TTNB to choose the method of guidance. While US-TTNB has a high sensitivity and a low complication rate overall for pleural and pulmonary lesions with pleural contact, our study suggests US-TTNB may not be the optimal approach for lesions with < 10–15 mm of pleural contact length.

The influence of pleural contact length on the sensitivity and safety of US-TTNB likely reflects increased technical difficulty using US guidance when a lesion has little contact with the pleura. Indeed, the area with pleural contact provides the acoustic window in which we can visualize the lesion and complete the US-TTNB [6]. Consistently, lesion size, core needle diameter of 18G, and chest wall invasion positively influenced the sensitivity of US-TTNB in our study but were not independently associated in multivariate analysis, possibly because these variables were associated with a concomitant increase in pleural contact length. The occurrence of a pneumothorax lowered the sensitivity of US-TTNB, which is not surprising because pneumothorax generally precludes any tissue sampling due to the loss of the acoustic window.

In our analyses, we used cubic splines, a curve fitting method not frequently applied in biomedical research, to provide clinical guidance in decision making when performing US-TTNB. Cubic splines, in which distinct polynomials are fitted for each data window, are a useful way to model complex nonlinear relationships between continuous variables and outcomes, avoiding arbitrarily splitting a continuous variable into categories or the forced assumption of a linear association [24]. Using this method, we observed a significant increase in US-TTNB sensitivity as pleural contact length increased up to ~30mm, whereas the pneumothorax rate exhibited the opposite relationship, reflecting the technical difficulty of US-TTNB for small lesions with limited pleural contact. Altogether, this resulted in a relatively linear increase in the sensitivity/pneumothorax rate ratio as the pleural contact length increased. While this ratio rises reasonably from ~3.5, ~6, to ~17 as the pleural contact length increases from 20, 30, to 125 mm, respectively, relying on US-TTNB appears ill-advised for lesions < 10 mm where the risk of pneumothorax is as high as the chance of obtaining diagnosis. The cubic spline analyses were essential in quantitating the relationships between pleural contact length, TTNB sensitivity, and pneumothorax rates.

We believe the results of this study may have major clinical impacts including triage based on pleural contact length to determine the guidance method for TTNB, given that diagnostic yield and pneumothorax are both influenced by this same key variable. Our institution has already adopted such a triage method; our radiologists review all TTNB requests and determine an appropriate guidance method based on pleural contact length. However, from this study, we also know that the sensitivity of

Table 4 Variables affecting pneumothorax rates

Variables	Univariate Odds ratio (95% CI)	*p* value	Multivariate* (without lesion size) Odds ratio (95% CI)	*p* value	Multivariate* (without pleural contact length) Odds ratio (95% CI)	*p* value
Pleural contact length, per mm	0.98 (0.97–0.99)	< 0.001	0.98 (0.97–0.99)	0.013		
Lesion size, per mm	0.97 (0.96–0.98)	< 0.001			0.98 (0.96–0.99)	0.006
Apical location	0.33 (0.17–0.63)	< 0.001	0.57 (0.26–1.25)	0.160	0.50 (0.23–1.09)	0.080
Needle size (core), 18G vs 20G	0.37 (0.21–0.66)	< 0.001	0.47 (0.26–0.83)	0.010	0.48 (0.26–0.87)	0.015
Chest wall invasion	3.79 (0.85–16.9)	0.081				
Diaphragmatic contact	0.94 (0.50–1.75)	0.840				
Radiologist experience, per year	1.00 (1.00–1.00)	0.856				
Number of transthoracic passages	0.72 (0.51–1.01)	0.054				
Medical resident involvement	0.94 (0.59–1.51)	0.800				
Emphysema	0.99 (0.59–1.67)	0.985				
FEV1	0.99 (0.99–1.01)	0.679				

FEV1, forced expiratory volume in 1 s

*The two multivariate models for pneumothorax were built with all of the US-TTNB (n = 528). This series revealed high collinearity between size and pleural contact length (correlation coefficient = 0.76; R^2 = 0.58). Therefore, one model excluded lesion size and the other excluded pleural contact length

US-TTNB increases only up to 30 mm of pleural contact length providing an important refinement to our local triage algorithm. Pre-procedure assessment of pleural contact length may maximize the potential of US guidance in TTNB, given its previously reported advantages such as a shorter duration of the procedure [10, 11, 25, 26], a shorter delay before the procedure [10, 13, 25], and its cost-effectiveness [10].

Our observed sensitivity of 72% is consistent with the sensitivity (79–89%) reported by Guo and colleagues, which to our knowledge is the only other large study of US-TTNB (n = 648) [27]. Furthermore, in Guo's study, sensitivity dropped to 54–79% in lesions that were ≤ 20 mm in size, which is consistent with our findings. However, our results differ from those seen in previous studies of smaller cohorts (n = 16 to 150) [10, 11, 26, 28–39]. A pooled analysis by DiBardino and colleagues of 518 US-TTNB assessed in these small studies suggested a sensitivity of 92% but may reflect a publication bias among US-TTNB studies. Additionally, the inclusion of mediastinal and chest wall lesions can heavily impact the sensitivity measured in small studies. In fact, preliminary data from our institution indicate that US-TTNB has a sensitivity of 86% for mediastinal malignant lesions and 91% for chest wall malignant lesions and suggests that the sensitivity in this study would be higher if chest wall and mediastinal lesions had been included in the analysis [40, 41]. Moreover, the sensitivity of 72% in the present study may be explained by a short median pleural contact length in the cohort, only 32 mm (IQR 18–61). Consistent with this hypothesis, Jeon and colleagues [39] also reported that pleural contact length correlated positively with sensitivity, resulting in a sensitivity of 86% in their series of 97 US-TTNBs with a median lesion size of 46 mm (IQR 30–70).

The complication rate in the present study is comparable with that in the previous series, with pneumothorax and hemorrhagic complications occurring in 15% and 3% of patients, respectively. Intriguingly, the use of a biopsy needle with 18G diameter was associated with a significantly lower pneumothorax rate than the use of a 20G needle. This finding was unexpected [15, 42] and potential confounding variables, such as the smaller needle being used for core biopsy of smaller lesions, could not fully explain this association based on our multivariate analysis. As this finding is counterintuitive, it is likely that unidentified confounding variables influenced pneumothorax rates. Further study is needed to understand this observation.

This study is limited by its retrospective design, which could have potentially led to selection and reporting bias. Moreover, we had limited description of the involvement of the medical residents during the US-TTNBs, leading to potential misclassification. Finally, a small proportion of patients did not have their diagnosis confirmed by a pathological report, which is consistent with a significant proportion of patients being diagnosed at an advanced stage of the disease. This proportion is also consistent with previous series [22, 23]. Although pathological confirmation of every diagnosis would be ideal in determining the sensitivity, our use of a composite criterion using clinical and radiological follow-up as the reference standard has been validated in prior TTNB studies [22, 23].

Conclusion

US-TTNB has a high sensitivity and a low complication rate for pleural and pulmonary lesions with pleural contact. Importantly, this study confirms that pleural contact length is

a key variable predicting the sensitivity of US-TTNB and the pneumothorax rate following US-TTNB. The study provides important refinements of previous studies due to the large number of patients studied and the novel approach to curve fitting for data analysis. Because US guidance has several advantages as compared with CT guidance, US-TTNB should be a procedure of choice to biopsy peripheral lung and pleural lesions with significant pleural contact. Conversely, relying on US-TTNB to diagnose lesions < 10–15 mm appears questionable.

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Declarations

Guarantor The scientific guarantor of this publication is Simon Lemieux.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry Kevin F. Kennedy kindly provided statistical advice for this manuscript.

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Ethical approval Institutional Review Board approval was obtained (#2018-3032, 21593).

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in a prior abstract presentation of this work which occurred at the 2019 RSNA Annual Meeting in Chicago, IL, on December 1, 2019. Our manuscript has no overlap with prior previously published work.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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