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ORIGINAL ARTICLE

Diagnostic yield of non-guided flexible bronchoscopy for peripheral pulmonary neoplasia

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Abstract

Background: The role of conventional bronchoscopy for peripheral pulmonary neoplasia remains controversial. We aimed to assess the diagnostic yield and the added value of non-guided bronchial aspiration, bronchoalveolar lavage (BAL), and brushing for the diagnosis of pulmonary neoplasia not visible endoscopically.

Methods: We retrospectively assessed 207 consecutive patients with a final diagnosis of peripheral lung malignancy who underwent bronchoscopy with non-guided aspiration, brushing, and BAL as their initial evaluation. The influence of clinical and radiological factors on diagnostic yield was assessed using univariate logistic regression analyses.

Results: The overall sensitivity of non-guided bronchoscopy was 25.6%, whereas sensitivities for bronchial aspiration, BAL, and brushing were 14.2%, 11.6%, and 16.5%, respectively. Younger age, larger lesion, central/intermediate distance from the hilum, presence of a bronchus sign, and higher standardized uptake value (SUV) on positron emission tomography scan were predictors of a higher diagnostic yield. Conversely, forced expiratory volume in one second, fellow implication in the procedure, and tumor histology did not influence sensitivity. The overall sensitivity of bronshoscopy was >40% for tumors >4 cm, located in the central/intermediate thirds of the lung, showing a bronchus sign, with an SUV >12 or occurring in patients <50 years of age. Conversely, the sensitivity was <10% for tumors <2 cm, located peripherally or with an SUV <4.

Conclusion: Neoplasia characteristics may help targeting situations in which conventional bronchoscopy could be used as the initial diagnostic procedure when advanced techniques are unavailable. However, advanced diagnostic tools should probably be proposed as the initial modality for the diagnosis of peripheral malignant lesions when available.

Introduction

Peripheral pulmonary lesions are common clinical problems and most are detected incidentally on chest X-rays or computed tomography (CT) scans.[1] Recent data suggesting a mortality benefit with low-dose CT screening for lung cancer may eventually lead to a significant increase in patient referral for the evaluation of peripheral pulmonary nodules.[2]

Guidelines from the American College of Chest Physicians stress the value of risk factor assessment for guiding subsequent investigations of peripheral pulmonary lesions.[3,4] Surgical resection is favored for lesions at high risk of malignancy (grade of recommendation 2C), whereas radiological follow-up is preferred for low risk lesions (grade 2C). For patients with intermediate risk lesions, additional tests are recommended, which should be selected based on nodule size, location, relation to a patent airway, risk of complications in the individual patient, and available expertise. CT scan-guided transthoracic needle aspiration (TTNA) is generally preferred for nodules located in proximity of the chest wall or for deeper lesions, provided that fissures do not need to be traversed and there is no surrounding emphysema. On

the other hand, bronchoscopic techniques are favored for nodules located in proximity to a patent bronchus and in individuals who are at high risk for pneumothorax following TTNA. For peripheral nodules, radial endobronchial ultrasound (EBUS) guided biopsy and electromagnetic navigation guidance are recommended (grade 1C) if available and TTNA is also a diagnostic option (grade 1B).[5] That said, because of delays in access and risks associated with TTNA, as well as unavailability of advanced diagnostic techniques in most centers, conventional bronchoscopy is still performed for many patients with peripheral pulmonary lesions. However, the role of non-guided bronchoscopy in the initial evaluation is not well established.[6]

Therefore, the goal of our study was to document the overall sensitivity of standard bronchoscopy without fluoroscopic/ultrasound guidance for peripheral lung malignancy not visible endoscopically and to compare the diagnostic performance of individual sampling techniques including bronchial aspiration, brushing, and bronchoalveolar lavage (BAL). We also aimed to identify clinical and radiologic factors predictive of an improved diagnostic yield.

Methods

We retrospectively reviewed medical records of all consecutive patients who underwent a conventional bronchoscopy for peripheral pulmonary lesions at the *Institut universitaire de cardiologie et de pneumologie de Québec* between April 2008 and December 2010, for whom the final diagnosis was a neoplasia. Criteria for inclusion in the study were: (i) presence of a circumscribed solid lung lesion not visible endoscopically (pure ground glass opacities were excluded); (ii) bronchoscopy performed with bronchial aspiration, brushing, and BAL; and (iii) a final pathologic diagnosis of lung cancer established by either bronchoscopy or any other diagnostic procedure.

Flexible bronchoscopy (BF P180, 4.9 mm, Olympus, Richmond Hill, ON, Canada) was performed as part of the initial diagnostic workup under conscious sedation using a combination of midazolam and fentanyl. Secretions present in the bronchial tree were aspirated for cytologic examination; when no secretions were present, the lobar bronchus was washed with one or two aliquots of 10 mL of saline. Based on axial CT images, blinded brushing was performed by introducing a brush (1.9 mm, Boston Scientific, Spencer, IN, USA) in the target segmental bronchus. BAL was performed by injecting three aliquots of 50 mL of saline with the bronchoscope in a wedged position in the involved segment. For bronchial brushing, the brush was smeared on two slides, which were then immediately fixed with 95% ethyl alcohol. The samples from both bronchial aspiration and BAL were preserved in 50% ethyl alcohol. The specimens were centrifuged for five minutes at 1500 revolutions per minute. Two to four slides were prepared from cell concentrate. All slides were stained with Papanicolaou stain. When malignant cells were identified, the residual specimen was used to prepare a cellblock by resuspending the cell pellet in 10% formalin for 24 hours and then in 3% agarose. A section of 5 μm thickness was then obtained. Routine hematoxylin and eosin staining was used on cellblock sections and, when necessary, immunohistochemical stainings were performed to phenotype the tumoral cells. Cytology results clearly diagnostic for lung cancer were classified as positive, while results with non-diagnostic material, benign, atypical or suspicious cells without a certain diagnosis were classified as negative. None of the patients experienced pneumothorax. All analyses were performed in accordance with the *Institut Universitaire de Cardiologie et de Pneumologie de Québec* biosafety and ethics committee (CER-21034).

Statistical analysis

Categorical data are expressed as proportions and numerical data as mean ± standard deviation. Differences in proportions were tested with the Chi-square or Fisher's exact tests. Continuous variables were compared with the Student *t*-test with the Welch correction depending on equal or unequal variances. The influence of various clinical and radiologic factors on sensitivity was first assessed using univariate logistic regression models including patient's age, forced expiratory volume in 1 second (FEV1), fellow implication in the procedure, lesion size, hypermetabolism on positron emission tomography (PET) scan, distance of the lesion from the hilum (lesions within the inner and middle third vs. outer third of the hilar-costal distance as determined on axial CT images), the presence of a bronchus sign (an air-filled bronchus leading to the lesion), and pathology. Continuous variables were checked for the assumption of linearity in the logit using quartiles of the distribution and fractional polynomials before building the model in order to obtain the correct relationships. Furthermore, in order to appreciate the appropriate functional form between predictors of a higher diagnostic yield for the three techniques and continuous variables, a generalized additive model was built using the binary distribution. Smoothing was performed by spline fitting (df = 4) to investigate inflection point, which cannot be identified using linear models. Age and lesion size had these knots for some predictors to respect the linearity in the logit before and after the inflection point. The results were considered significant with P values ≤ 0.05. Data were analyzed using the SAS v9.1.3 statistical package (SAS Institute Inc., Cary, NC, USA).

Results

Two hundred and seven patients fulfilled the inclusion criteria and were included in the study. Patients' characteristics are

Table 1 Characteristics of the 207 cases

Gender – no. (%)	
Men	108 (52.2%)
Women	99 (47.8%)
Age – mean ± SD (range), years	66 ± 9 (40–85)
Smoking status – no. (%)	
Smokers	190 (91.8%)
Non-smokers	17 (8.2%)
FEV1 – mean ± SD (range), % (n = 179)	87 ± 20 (30–132)
Bronchoscopist – no. (%)	
Respirologist	138 (66.7%)
Fellow	69 (33.3%)
BAL fluid return – mean ± SD (range), mL (n = 109)	37 (1–90)
Lesion size – mean ± SD (range), cm	3.3 ± 1.8 (0.8–10.2)
SUV on PET scan – mean ± SD (range) (n = 176)	9.2 ± 6.5 (1.0–34.1)
Distance from the hilum – no. (%) (n = 205)†	
Central/intermediate	94 (45.9%)
Peripheral	111 (54.1%)
Bronchus sign – no. (%) (n = 205)	
Present	49 (23.9%)
Absent	156 (76.1%)

†Lesions within the inner, middle, and outer thirds of the hilar-costal distance on computed tomography scan were classified as central, intermediate or peripheral, respectively. BAL, bronchoalveolar lavage; FEV1, forced expiratory volume in one second; PET, positron emission tomography; SD, standard deviation; SUV, standardized uptake value.

Table 2 Diagnostic method and final diagnosis

	n	%
Final diagnostic method		
Bronchoscopy	53	25.6%
Guided transbronchial biopsy	8	3.9%
Lymph node biopsy with EBUS	6	2.9%
Transthoracic fine-needle aspiration biopsy	94	45.4%
Sampling from distant metastasis	8	3.9%
Mediastinoscopy	3	1.4%
Thoracoscopy	35	16.9%
Pathology		
NSCLC†	185	89.4%
Others‡	22	10.6%
Stage		
Limited§	129	62.3%
Extensive¶	78	37.7%

†Adenocarcinoma (n = 142), squamous cell carcinoma (SCLC, n = 28), and non-small cell lung carcinoma (NSCLC) not otherwise specified (n = 15). ‡Small cell lung carcinoma (n = 10), carcinoid tumor (n = 9), sarcomatoid carcinoma (n = 1), fusiform cell sarcoma (n = 1), mucinous cystadenocarcinoma (n = 1). §Limited SCLC and stages 1a, 1b, 2a, 2b NSCLC. ¶Extensive SCLC and stages 3a, 3b, 4 NSCLC. EBUS, endobronchial ultrasound.

described in Table 1. In 20 patients, brushing was not performed or the brushing cytologic specimen was judged not satisfactory. These patients did not differ in terms of age, smoking status and FEV1, bronchoscopist, presence/absence of bronchus sign, tumor pathology, location, size or standardized uptake value (SUV) (all $P > 0.20$). As a conservative approach, these brushings were considered as negative.

The overall sensitivity of non-guided bronchoscopy for malignancy was 25.6% (53/207 patients). In the other 154 patients, the diagnosis was established most frequently by TTNA (Table 2). The sensitivities of individual sampling techniques were 14.2% for bronchial aspiration, 11.6% for BAL, and 16.5% for brushing. Only BAL and brushing were statistically different ($P = 0.003$). When the individual contributions of each technique were compared to the diagnostic performance of bronchoscopy, brushing had the highest added yield, although the differences between the various techniques were not statistically significant ($P = 0.08$) (Fig 1).

In univariate analysis, younger age, larger lesion size, central/intermediate distance from the hilum, presence of a bronchus sign, and higher SUV on PET scan were predictors of a higher overall diagnostic yield (Table 3). Conversely, FEV1, fellow implication in the procedure, and tumor histology did not influence sensitivity. Interestingly, the influence of lesion size and patient age was not linear. In fact, an increased overall diagnostic yield was observed with

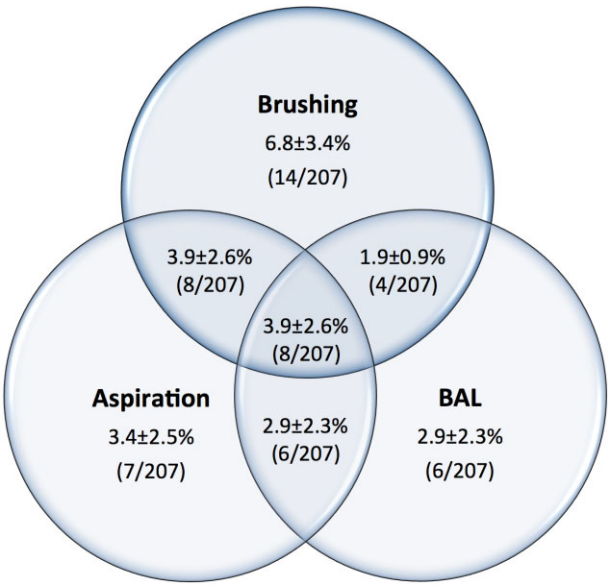

Figure 1 A summary of the diagnostic yield of bronchial aspiration, brushing, bronchoalveolar lavage (BAL), and their combination for non-endobronchial lung neoplasia. The overall diagnostic yield of non-guided bronchoscopy using these techniques was 25.6%. Brushing tended to be associated with the highest diagnostic yield (16.4%), compared to aspiration (14.0%) and BAL (11.6%), as well as the highest added yield, although the differences between the various techniques were not statistically significant ($P = 0.08$).

Table 3 Predictors of a higher diagnostic yield

	BAL OR (95% CI)	Bronchial aspiration OR (95% CI)	Brushing OR (95% CI)	Overall OR (95% CI)
Age†				
Age, per year			0.95 (0.91–0.99)‡	
≤50, per year	0.65 (0.45–0.94)§	0.65 (0.46–0.92)§		
>50, per year	0.98 (0.93–1.04)	1.01 (0.95–1.06)		
≤70, per year				0.92 (0.88–0.97)‡
>70, per year				1.06 (0.95–1.19)
FEV1, per %	1.02 (0.99–1.04)	1.00 (0.98–1.02)	1.00 (0.98–1.02)	1.00 (0.98–1.02)
Bronchoscopist, fellow *versus* respirologist	0.36 (0.12–1.11)	1.07 (0.47–2.45)	1.11 (0.51–2.43)	1.06 (0.54–2.08)
Lesion size¶				
Size, per cm		1.37 (1.13–1.66)‡		
≤3 cm, per cm	4.00 (1.23–13.00)§			3.24 (1.60–6.58)‡
>3 cm, per cm	1.11 (0.88–1.46)			1.01 (0.80–1.28)
≤4 cm, per cm			2.10 (1.31–3.37)‡	
>4 cm, per cm			0.75 (0.50–1.12)	
Distance from the hilum, central/intermediate *versus* peripheral	2.64 (1.08–6.48)§	2.51 (1.10–5.71)§	5.96 (2.43–14.6)‡	6.38 (3.05–13.32)‡
Presence of a bronchus sign, yes *versus* no	3.89 (1.62–9.37)‡	2.61 (1.15–5.95)§	2.85 (1.29–6.32)‡	2.95 (1.46–5.97)‡
SUV, per unit	1.06 (0.99–1.14)	1.07 (1.00–1.14)§	1.07 (1.01–1.14)§	1.09 (1.03–1.15)§
Pathology, NSCLC *versus* other	2.98 (0.38–23.20)	1.05 (0.29–3.80)	4.16 (0.53–32.36)	1.11 (0.38–3.25)

†The influence of patient age was not linear for bronchoalveolar lavage (BAL), aspiration, and the combination of diagnostic techniques. In fact, a decreased diagnostic yield was observed with increasing age up to 50 years for BAL and bronchial aspiration, after which point age had no effect on diagnostic performance. The overall diagnostic yield decreased with increasing age up to 70 years, after which point age had no effect on diagnostic performance. ‡$P < 0.01$; §$P < 0.05$. ¶The influence of lesion size was not linear for BAL, brushing, and the combination of diagnostic techniques. In fact, an increased overall diagnostic yield was observed with increasing lesion size up to a diameter of 3 cm and 4 cm for BAL and brushing, respectively, after which point it had no effect on diagnostic performance. The overall diagnostic yield increased with increasing lesion size up to a diameter of 3 cm. FEV1, forced expiratory volume in one second; NSCLC, non-small cell lung carcinoma; SUV, standardized uptake value.

increasing lesion size up to 3 cm in diameter, after which point size had no effect on diagnostic performance. Regarding the effect of age, although the yield decreased in older patients, age had no influence on diagnostic performance in patients of 70 years and older. The overall sensitivity of bronchoscopy was more than 40% for tumors >4 cm, located in the central/intermediate thirds of the lung, showing a bronchus sign, with an SUV >12 or occurring in patients <50 years of age. Conversely, the diagnostic yield was less than 10% for tumors <2 cm, located peripherally or with an SUV <4 (Fig 2).

Discussion

In this cohort of patients with pulmonary neoplasia not visible through conventional bronchoscopy, non-guided bronchoscopy without transbronchial biopsy had a sensitivity of 25.6%, with the highest yield provided by brushing. Higher diagnostic yield was also associated with younger age, larger lesions located in the central/intermediate thirds of the lung, presence of a bronchus sign, and higher SUV on PET scan.

In the present study, the overall sensitivity of bronchoscopy for the diagnosis of lung neoplasia not visible endoscopically was comparable to previous studies evaluating non-guided conventional bronchoscopy without transbronchial biopsy (6–33%).[7–12] While some studies suggested a global sensitivity of 78% for bronchoscopy in the diagnosis of lung cancer,[5] fluoroscopic guidance was used[13–25] and transbronchial biopsies were performed[26–39] in the vast majority of these studies. In addition, some of those series also included endobronchial lesions and benign lesions. In concordance with previous studies, larger lesion size, distance from the hilum, and presence of a bronchus sign were predictors of a higher sensitivity. Interestingly, the mean lesion size in the present study was higher (3.3 cm) than in previous series. Despite this, the overall sensitivity remained limited. This may be explained by the fact that beyond a certain point (3–4 cm in the current study), the sensitivity of bronchoscopy reaches a plateau, possibly because large lesions not visible endoscopically may be associated with necrotic neoplastic cells, post-obstructive pneumonia, and bronchial compression that could diminish bronchial aspiration, brushing, and BAL diagnostic yield. Another likely explanation is that the brush did not reach the lesion correctly as the lesion size was lower because of inadequate airway selection given the absence of guidance. We also identified new variables increasing the diagnostic yield of bronchoscopy, including higher SUV and younger age.

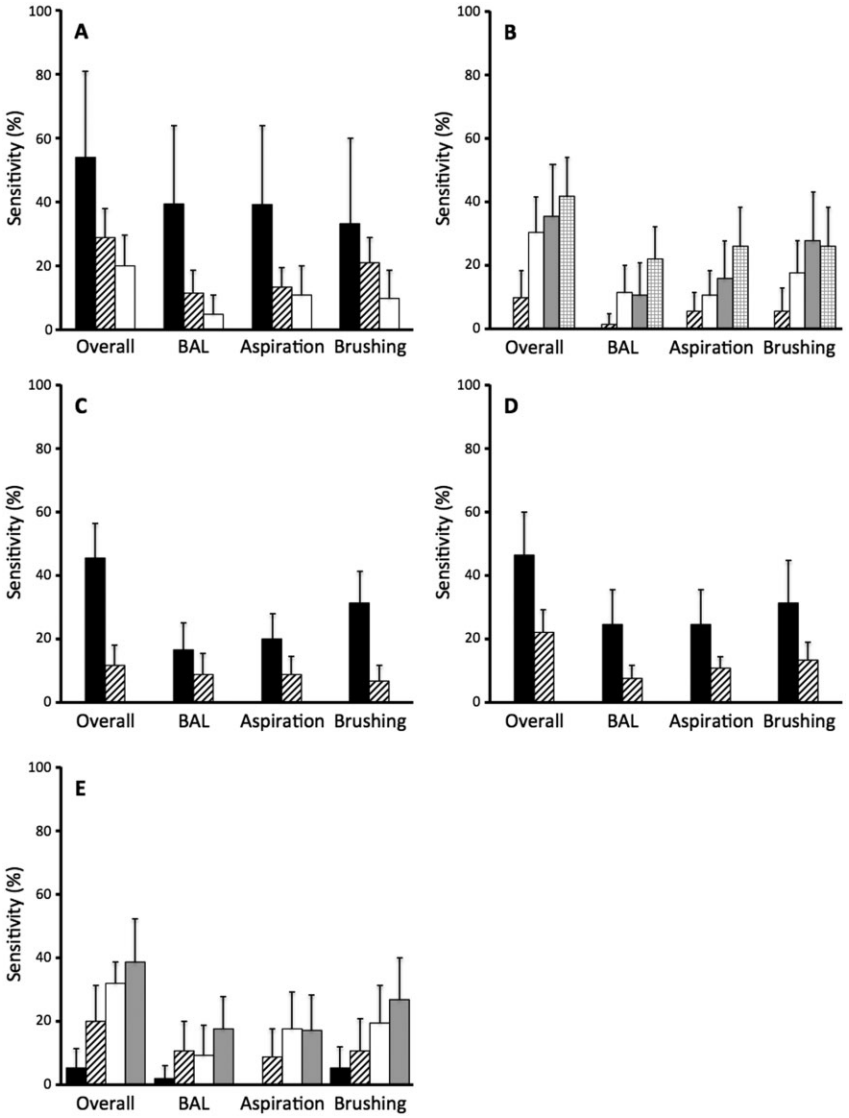

Figure 2 Diagnostic yield of bronchial aspiration, brushing, bronchoalveolar lavage (BAL) and their combination for non-endobronchial lung neoplasia according to: (**a**) patients' age; (**b**) tumor size; (**c**) distance from the hilum; (**d**) presence or absence of bronchus sign; and (**e**) standardized uptake value (SUV) on positron emission tomography. Diagnostic yield is described as sensitivity with 95% confidence interval. ■, ≤50 years; ▨, 51–70 years; □, >70 years; ■, ≤1 cm; ▨, 1.1–2 cm; □, 2.1–3 cm; ▩, 3.1–4 cm; ⊞, >4 cm; ■, central-intermediate; ▨, peripheral; ■, bronchus; ▨, no bronchus sign; ■, SUV ≤ 4; ▨, SUV 4.1–8; □, SUV 8.1–12; ▩, SUV > 12.

Conversely, the histology of lung cancer did not influence the diagnostic yield of bronchoscopy.

While brushing tended to have more added value over aspiration and BAL, the three diagnostic modalities were complementary in improving the yield of bronchoscopy for peripheral lung cancer (Fig 1), as previously suggested.[40–42] However, among patients with lung cancer and based on the added diagnostic value of each technique, the number of procedures needed to diagnose one extra patient with lung neoplasia not visible endoscopically was 15 (95% confidence interval [CI] 10–29), 29 (95% CI 17–111), and 34 (95% CI 19–167) for brushing, bronchial aspiration, and BAL, respectively. Because BAL is the most costly technique (≈$160 USD for material, specimen processing, and pathologist fees, compared with ≈$90 USD for other techniques), the minimal estimated cost for each additional diagnosis of peripheral lung cancer was ≈$1350 USD ($900-$2610 USD), $2610 USD ($1530-$9990 USD), and $5440 USD ($3040-$26 720 USD) for brushing, bronchial aspiration and BAL, respectively, in addition to the cost of flexible bronchoscopy. Therefore, the cost-effectiveness of including all three techniques for each exam is questionable, especially for lesions with features associated with low diagnostic yield (Fig 2). Sequential specimen processing might be a more cost-effective alternative,

where the lab processes BAL only if other specimens are non-diagnostic.[43] Moreover, patients with peripheral lesions less than 2 cm should probably be referred for more advanced diagnostic modalities as non-guided bronchoscopy is associated with a diagnostic yield of <5–10% and significant costs. This is especially important with the development of lung cancer screening strategies because most early stage cancers detected by CT-based screening programs are <2 cm.[44] Prospective cost-effectiveness analyses are required to determine whether such patients should be directly referred for TTNA or advanced guided bronchoscopy techniques. Bronchocoscopy should also be delayed after PET scanning as tumor stage and SUV may dictate the most appropriate diagnostic technique. Ultimately, the development of predictive tools based on patient and lesion characteristics are necessary to accurately estimate the probability that lung nodules are malignant and for which immediate lung resection may be proposed in low-risk surgical candidates, especially if sublobar resections are proved as effective as lobectomy for early-stage lung cancer.[44] Conversely, the diagnostic yield of standard bronchoscopy reaches up to 45% for larger and centrally located neoplasia not visible during endoscopy, especially when a bronchus sign is present. While advanced guided bronchoscopy techniques have been associated with increased diagnostic yield, their cost-effectiveness is yet to be determined in these circumstances.

An important limitation of our study is its size, which limited our ability to detect subtle differences between the various sampling techniques. Moreover, the low number of patients diagnosed with each technique precluded building a valid multivariate regression model to adjust the univariate analyses for potential confounders. In addition, the retrospective nature of our analysis is associated with its inherent limitations. Finally, the results of this study are difficult to apply to a population with undifferentiated peripheral pulmonary lesions because only malignant lesions were included.

Conclusion

Given the limited sensitivity of bronchoscopy without guidance for the diagnosis of peripheral malignant lesions not visible endoscopically, advanced diagnostic modalities, such as radial EBUS, TTNA or even video-assisted thoracoscopic surgery, should be favored as the initial diagnostic modality when available. However, some clinical variables are predictors of a higher diagnostic yield and could help targeting situations in which bronchoscopy could be used as the initial test when advanced techniques are unavailable, namely larger lesions showing a bronchus sign and located in the central/intermediate thirds of the lung. Finally, the routine use of BAL is questionable as it is probably not cost-effective when added to bronchial brushing and aspiration.

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Disclosure

No authors report any conflict of interest.

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