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ORIGINAL ARTICLE

Diagnostic utility of peripheral endobronchial ultrasound with electromagnetic navigation bronchoscopy in peripheral lung nodules

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ABSTRACT

Background and objective: **This study aimed to investigate the diagnostic utility of peripheral endobronchial ultrasound (pEBUS) followed by as-needed electromagnetic navigation bronchoscopy (ENB) for sampling peripheral lung nodules.**
Methods: **The study was a single-arm, prospective cohort study of patients with peripheral lung nodules. Peripheral lung lesion localization was initially performed using a pEBUS probe with guide sheath. If localization failed with pEBUS alone, ENB was used to help identify the lesion. Transbronchial biopsy, bronchial brush, transbronchial needle aspiration and bronchial washings were performed.**
Results: **Sixty patients were enrolled with average lesion size of 27 mm and mean pleural distance of 20 mm. Lesions were found with pEBUS alone in 75% of cases. The addition of ENB improved lesion localization to 93%. However, diagnostic yield for pEBUS alone and pEBUS with ENB were 43% and 50%, respectively. Factors predicting need for ENB use included smaller lesion size and absence of an air bronchus sign on computed tomography.**
Conclusions: **ENB improves localization of lung lesions after unsuccessful pEBUS but is often not sufficient to ensure confirmation of a specific diagnosis. Technical improvements in sampling methods could improve the diagnostic yield.**

Key words: bronchoscopy, electromagnetic navigation, endobronchial ultrasound, lung cancer, solitary pulmonary nodule.

Abbreviations: CT, computed tomography; ENB, electromagnetic navigation bronchoscopy; pEBUS, peripheral endobronchial ultrasound.

SUMMARY AT A GLANCE

Peripheral pulmonary nodules were evaluated with sequential use of EBUS and electromagnetic navigation. Although successful in localizing lesions, the diagnostic yield was low. Procedural learning may impact the diagnostic yield and additional biopsy tools may be beneficial.

INTRODUCTION

Diagnostic differentiation of peripheral lung nodules remains a challenge for pulmonary physicians. Nodules separated from the pleural surface face an elevated risk of pneumothorax with transthoracic needle aspiration,[1] while conventional bronchoscopy for nodules <2 cm has a limited diagnostic yield of 10–50%.[2] Newer techniques such as peripheral endobronchial ultrasound (pEBUS) and electromagnetic navigation bronchoscopy (ENB) have been shown to increase the diagnostic yield to as high as 88% when used in combination.[3]

Combining pEBUS and ENB can overcome the limitations of each technique by using ENB to plan and navigate to the peripheral lesion followed by pEBUS imaging through the guide sheath confirming that the lesion has been localized. Unfortunately, the routine use of these techniques is relatively expensive and real-time confirmation of nodule localization with pEBUS does not always result in a diagnostic result.[4–12]

This prospective study was designed to investigate factors which may predict the need to use ENB in addition to pEBUS versus pEBUS alone, and to determine factors associated with the 'diagnostic gap' between lesion identification and diagnostic yield.

METHODS

The study was designed as a prospective, non-randomized single-arm cohort study carried out in

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two different centres. Subjects with peripheral pulmonary lesions undergoing bronchoscopy for tissue diagnosis were considered for inclusion if they fulfilled the following criteria: age over 16 years, lung nodule(s) identified on computed tomography (CT), clinical decision to obtain a tissue biopsy of the lung lesion, CT-guided biopsy not the preferred technique (due to technical difficulty) or a previously negative CT-guided biopsy. Exclusion criteria were: an inability to obtain informed consent in English; a lesion less than 1 cm or greater than 6 cm in long axis; significant mediastinal or hilar lymphadenopathy (>2 cm on short axis on chest CT); suggestion of an endobronchial abnormality on chest CT; a medical contraindication to bronchoscopy; an implanted electronic medical device; confirmed or suspected pregnancy; uncontrolled coagulopathy or a clinical decision to surgically resect the lesion with a high suspicion for lung cancer.

Written, informed consent was obtained from all study participants and the protocol was approved at both institutions by the University of Calgary Conjoint Health Research Ethics Board and the Research Ethics Committee of the Institut Universitaire de Cardiologie et de Pneumologie de Québec, respectively. The trial was registered in the clinicaltrials.gov Protocol Registration System (NCT00925210).

All patients underwent CT (slice thickness <1.25 mm, 0.75 mm overlap) for ENB planning with identification of the target lesion, airway path and registration points prior to the bronchoscopy. Nodules were classified on CT by the location of the nearest air bronchus (modified from the Tsuboi classification[13]). Virtual bronchoscopy was carried out for navigation planning prior to the procedure in all patients (Bronchus V4.3.4, SuperDimension, Minneapolis, MN, USA). In the bronchoscopy suite, all patients were placed on the electromagnetic board with continuous cardiac monitoring and oximetry. Supplemental oxygen was provided via nasal cannula or face mask to maintain oxygen saturation over 90%. Topical anaesthesia was provided with lidocaine and conscious sedation delivered with a combination of midazolam, fentanyl and/or propofol intravenously according to the operator's preferences.

Bronchoscopy was performed by one of six bronchoscopists using a 1T-160 (6 mm outer diameter, 2.8 mm channel) Olympus video bronchoscope (Olympus Canada, Markham, ON, Canada). Following complete airway examination, the pEBUS probe (UM-S20-20R, Olympus Canada) was used in a guide sheath (i-Logic Guide Catheter, SuperDimension) in an attempt to identify the lesion. The bronchoscope was advanced into the segment or subsegment of interest and the probe with guide sheath were advanced into the lung periphery under real-time ultrasound guidance. If needed, a double-hinged curette (model CC-6DR-1, Olympus Canada) could be used to direct the guide sheath. Repositioning of the probe and guide sheath was performed multiple times until the lesion was identified or the operator felt that no further attempts would be successful. If the lesion was identified on ultrasound, the relative probe location was described (within or adjacent to lesion) and a representative EBUS picture was printed.

If the lesion was not identified using pEBUS, then the pEBUS and guide sheath were removed and the ENB system (Bronchus V4.3.4, SuperDimension) was activated. The ENB probe and guide sheath were then inserted into the working channel of the bronchoscope and airway landmarks were registered with the virtual bronchoscopy system with a goal of a registration error <6 mm. The bronchoscope was then wedged into the segmental or subsegmental airway of interest and the ENB probe with guide sheath advanced towards the target lesion with ENB guidance. Once the ENB probe reached the lesion, the guide sheath was left in place while the ENB probe was removed and the pEBUS was inserted into the guide sheath to confirm its identification of the lesion. If the EBUS probe did not confirm lesion identification, then the ENB probe was again used until lesion identification was confirmed by EBUS.

Through the guide sheath, samples were obtained with at least four transbronchial biopsy passes, four transbronchial needle aspirates, one cytology brush and a mini-bronchoalveolar lavage through the guide sheath or a full bronchoalveolar lavage of the lung segment, in that order. Fluoroscopy was not used nor was rapid on-site examination. The operator performed sampling of other intrathoracic lesions during the same session according to the clinical situation. If lymph nodes >1 cm were detected on CT, then curvilinear EBUS was used during the same procedure to sample mediastinal/hilar lymph nodes prior to investigation of the peripheral lesion. The operator did not have knowledge of pathological mediastinal staging prior to investigation of the peripheral lesion. If the lesion was never identified with ENB and EBUS, then a bronchoalveolar lavage of the segmental airway of the lesion was performed.

Routine posteroanterior and lateral chest radiographs were carried out within 2 h after the procedure. For non-diagnostic lesions, the next course of action was determined by the patient and their physician. If no additional sampling technique was pursued, then the patient's lesion was followed for at least 1 year with CT to ensure stability.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS, version 19, IBM, Chicago, IL, USA). A sample size of 60 subjects was selected in order to achieve a 95% confidence interval of $\pm$ 7.5% around the diagnostic yield of the combined approach. Multinomial regression analysis was carried out using the following factors: Age, Tsuboi classification, use of ENB, pathological diagnosis, air bronchus sign present, pEBUS positioning within lesion, and operator; lesion size and distance from costal pleural were covariates for the analysis. Comparisons between diagnostic yield and localization success between the pEBUS and pEBUS + ENB procedures were computed with the McNemar's test, assuming that pEBUS procedures where a lesion was not found would have been non-diagnostic without addition of ENB. Analy-

Table 1 Patient and nodule characteristic

	Study cohort	pEBUS alone	pEBUS + ENB
Total	60	45	15
M/F	29/31	23/22	6/9
Age (SD)	68 (11)	67 (11)	70 (11)
Lesion size (cm (SD))	2.7 (1.2)	3.0 (1.2)	2.2 (1.0) *
Distance from costal pleura (cm (SD))	2.0 (1.7)	2.2 (1.8)	1.5 (1.4)
Procedure time (min ± SD)	40.2 (15.0)	35.9 ± 14.1	52.4 ± 10.2 *
Anaesthetic use (dose ± SD)			
Lidocaine (mg)	391 ± 7.6	379 ± 76	427 ± 63 *
Midazolam (mg)	6.3 ± 2.2	6.0 ± 2.3	6.9 ± 2.1
Fentanyl (ug)	109 ± 58	102.5 ± 51.8	127.1 ± 73.4
Propofol (mg)	166 ± 82	160.0 ± 81.6	181.4 ± 88.4
Location (% of total)			
Right upper lobe	16 (27)	12 (27)	4 (27)
Right middle lobe	8 (13)	7 (16)	1 (7)
Right lower lobe	10 (17)	9 (20)	1 (7)
Left upper lobe	15 (25)	8 (18)	7 (47)
Lingula	2 (3)	1 (2)	1 (7)
Left lower lobe	9 (15)	8 (18)	1 (7)
Final histological diagnosis			
Malignant	51 (85%)	38 (84.4%)	13 (86.6%)
NSCLC	43	31	12
Carcinoid	3	3	0
Metastatic cancer	3	3	0
Lymphoma	1	0	1
L.G.	1	1	0
Benign	9 (15%)	7 (15.6%)	2 (13.3%)
Infection†	3	3	0
Granuloma	5	4	1
Other‡	1	0	1

*t-test $P < 0.05$, pEBUS vs pEBUS + ENB groups.
†Nocardia for two subjects, actinomyces.
‡Clinical stability > 1 year, refused repeat biopsy.
ENB, electromagnetic navigation bronchoscopy; L.G., lymphomatoid granulomatosis; pEBUS, peripheral endobronchial ultrasound; SD, standard deviation.

ses of variance and Pearson's chi-square test were used to evaluate possible statistical differences between operators and changes in diagnostic yield with air bronchus sign and EBUS image location. Direct comparisons between groups were accomplished with a Student t-test. Correlation between diagnostic yield and operator caseload was performed using a Spearman rank correlation. Yields between sampling techniques were analysed with Cochran's Q-test. A P-value < 0.05 was considered statistically significant.

RESULTS

One hundred eleven patients were screened for the study with 60 patients enrolled from July 2009 to August 2010. Significant mediastinal lymphadenopathy was the most common reason for exclusion. Patients' characteristics are described in Table 1. The average diameter of the lesions was 27 mm (range 11–59) with an average distance of 20 mm (range 0–66) to the costal pleura. There was a visible air bronchus within or through the lesion in 65% of cases (modified Tsuboi 1 & 2). The procedure was aborted in one case due to excessive coughing. A pulmonary or interventional pulmonary medicine fellow was present for 43/60 (72%) procedures. Final diagnoses for the lesions are in Table 1 with malignancy accounting for 85% of cases. The pneumothorax rate was 8% (5/60) with a chest tube required in two cases (3.3%). This rate was not altered by the additional use of ENB. There were no cases of bleeding requiring additional interventions.

The nodule was identified on ultrasound image by pEBUS alone in 75% (45/60) of cases, ENB used in 15 cases led to identification of 11 additional lesions and improved the lesion identification rate to 56/60 (93%, $P = 0.001$ vs pEBUS alone). For ENB cases, mean registration error was 6.1 ± 1.2 mm and the mean distance to target was 12.0 ± 6.4 mm. Lesions requiring ENB were smaller (2.2 cm vs 3.0 cm, $P < 0.05$), were less likely to have an air bronchus sign on CT (33% vs 76%, $P < 0.01$) and more likely to be in an upper lobe ($P < 0.05$). Distance from costal pleura was similar. Use of ENB lengthened the total procedure (35.9 min

Table 2 Diagnostic yield according to lesion characteristics

	Study cohort	pEBUS alone	pEBUS + ENB
Total	60	45	15
Overall yield: + result/total (%)	30/60 (50)	26/45 (58)	4/15 (27)
Adjusted yield (%)(n.s. vs pEBUS ENB)	—	26/60 (43)	—
Tsuboi classification[n.s.] : + result/total (%)			
1 (air bronchus within lesion)	14/25 (56)	13/22 (59)	1/3 (33)
2 (air bronchus through lesion)	7/14 (50)	7/12 (58)	0/2 (0)
3 (air bronchus adjacent to lesion)	7/14 (50)	4/8 (50)	3/6 (50)
No air bronchus visible	2/7 (29)	2/3 (67)	0/4 (0)
Air bronchus sign—Tsuboi 1 & 2 (%)	21/39 (54)	20/34 (59)	1/5 (20)
EBUS image: + result/total (%)			
Within lesion	21/33 (64)*	20/31 (65)	1/2 (50)
Adjacent to lesion	9/23 (39)	6/14 (43)	3/9 (33)
No lesion visualized	0/4 (0)	N/A	0/4 (0)
Final diagnostic method			
Bronchoscopic sampling of lesion	30 (50)	26	4
Convex EBUS-TBNA	2 (3)	2	0
CT-TTNA	6 (10)	4	2
Surgical resection	11 (18)	7	4
Clinical course consistent with malignancy	8 (13)	5	3
Regression or stability greater than one year	3 (5)	1	2

*Chi-square, $P < 0.05$ for study cohort.

n.s., no statistical significance.[13] —, not applicable; CT, computed tomography; ENB, electromagnetic navigation bronchoscopy; pEBUS, peripheral endobronchial ultrasound; TBNA, transbronchial needle aspiration; TTNA, transthoracic needle aspiration.

Table 3: Case characteristics by operator

Operator	1 ($n = 16$)	2 ($n = 15$)	3 ($n = 17$)	4 ($n = 2$)	5 ($n = 5$)	6 ($n = 5$)
Procedure time (min)	35.9	47.7	44.7	27.0	20.0	39.4
ENB used (%)	1 (6)	4 (27)	7 (41)	0 (0)	0 (0)	3 (60)
Air bronchus sign (%)	11 (69)	8 (53)	10 (59)	2 (100)	5 (100)	3 (60)
Lesion size ± SD	2.7 ± 1.3	2.9 ± 1.6	2.8 ± 1.0	4.1 ± 0.78	2.5 ± 0.72	2.3 ± 0.91
Distance to costal pleura ± SD*	3.3 ± 1.8	1.7 ± 1.2	1.6 ± 1.5	0.5 ± 0.7	0.78 ± 1.1	1.8 ± 2.0
Lesion identified on pEBUS/ENB (%)	16/16 (100)	13/15 (87)	16/17 (94)	2 (100)	5 (100)	4 (80)
Diagnostic yield (%)†	12 (75)	8 (53)	9 (53)	0 (0)	0 (0)	1 (20)

*ANOVA, $P < 0.001$.

†Chi-square, $P < 0.05$.

ENB, electromagnetic navigation bronchoscopy; pEBUS, peripheral endobronchial ultrasound; SD, standard deviation.

vs 52.4 min, $P < 0.05$) and required the use of more lidocaine. The dosages of sedative medications were not significantly different between groups.

Overall diagnostic yield was 50% (Table 2). Peripheral EBUS alone lead to a diagnosis in 26/45 (58%) cases, and 4/15 (27%) of cases requiring ENB—11 of which were confirmed on pEBUS—were diagnostic. Multinomial regression analysis revealed pEBUS probe location within the lesion and different operators as factors affecting diagnostic yield. The improvement in diagnostic yield with addition of ENB was not statistically significant over pEBUS alone (26/60 vs 30/60. $P = 0.125$). Lesions with positive bronchoscopic diagnosis trended to be larger (3.1 cm vs 2.5 cm, $P = 0.06$) but distance from costal pleura was similar and location (lobe) did not affect diagnostic yield. Diagnostic yield was highest when the EBUS probe was located within the lesion (within 64%, adjacent 39%, not found 0%, $P < 0.02$) (Table 2). The air bronchus sign (Tsuboi 1 & 2) on CT imaging was associated with the finding of pEBUS probe being within the lesion on EBUS but it did not in itself significantly alter the diagnostic yield (54% vs 43%, P = n.s.). Differences in diagnostic yield were noted between the six study bronchoscopists ($P < 0.05$, Table 3). There was a trend towards increasing diagnostic yield with operator caseload but this was not statistically significant ($P = 0.067$). Lesions further from the costal pleural also trended towards a higher diagnostic yield with a significant difference found with analysis of variance (based on operator) but was not significant with linear regression analysis (Table 3). No sampling technique was statistically superior than another (Table 4).

Table 4: Diagnostic yield for each sampling instrument

Diagnostic yield	BAL	Bronchial brush	Transbronchial biopsy	Transbronchial needle aspirate
ENB used (%)	2/15 (13)	2/15 (13)	3/15 (20)	3/15 (20)
ENB not used (%)	17/45 (38)	20/45 (44)	14/45 (31)	20/45 (44)
Sampling not performed (%)	1/60 (2)	3/60 (5)	3/60 (5)	6/60 (10)
Overall yield (%) n.s.	19/60 (29)	22/60 (37)	17/60 (28)	23/60 (38)
Sole positive test (%)	1/60 (2)	2/60 (3)	3/60 (5)	3/60 (5)

BAL, bronchoalveolar lavage; ENB, electromagnetic navigation bronchoscopy; n.s., no significant difference.

DISCUSSION

Our study demonstrates that a large proportion of peripheral lung lesions can be localized with the sequential use of pEBUS followed by immediate deployment of an ENB system if needed during the same procedure. This approach allowed us to limit the use of costly ENB disposables to 25% of cases while still achieving a 93% lesion localization rate. This lesion localization rate is at the very high end of the range of those reported for pEBUS alone in the literature.[7,9,11,14] Even in more difficult cases where pEBUS could not identify the lesion, the addition of ENB lead to the localization of the lesion in additional 18% of cases. Smaller lesions without air bronchus sign on CT were more likely to require ENB, a useful finding for bronchoscopists who can use these criteria to determine *a priori* if pEBUS alone will be adequate for a procedure, or if the added preparation, planning and cost of ENB are required. The pneumothorax rate of 8% is likely a reflection of the peripheral location of the lesions studied (2 cm from pleura) although this rate was similar to another study using combined ENB and pEBUS.[3]

Despite the high success rate in lesion localization, the diagnostic yield obtained was significantly lower at 50%, pointing to a significant 'diagnostic gap' between image localization and the establishment of a specific diagnosis. This modest diagnostic yield is difficult to explain on the basis of lesion characteristics such as size and prevalence of malignancy as suggested in previous reports, although 1/3 of the lesions in this study were ≤2.0 cm, a subgroup with reported yields as low as 18–30%.[6,15] Lesions in this series may have been more peripheral than in other studies, a factor which may reduce diagnostic rates,[16] but which has not usually been described. Case selection may play a role and direct comparisons of different case series may be limited because of difficulty in ensuring similar case mix of patients or lesions. Case selection even within our study may have resulted in the high variation in yield between different bronchoscopists despite the fact that trainees performed the majority of cases. It appeared that higher yields were obtained by more experienced operators as well as those with higher volume of cases and such is consistent with a previous study.[17] It may be appropriate to explain the difference in yield as part of a learning curve, but there was no difference in the ability of the operators to localize the lesions. Therefore, the difference would have been in the actual sampling of the lesion or perhaps navigation to a more favourable location in or near the lesion. ENB registration error less than 5 mm may improve diagnostic yield, but we were only able to accomplish this in 1/15 cases.[18] Improvement in registration with general anaesthesia[19] or with newer versions of the electromagnetic system may lead to improve performance. Fluoroscopy was not used but may have helped determine whether an instrument was displaced away from the lesion. However, we did often verify pEBUS localization between sampling techniques.

A diagnostic gap between pEBUS image localization and yield has been noted in other studies (8–23%),[4,6,7,14] albeit to a lesser degree than in ours. The diagnostic gap is even higher when pEBUS probe is adjacent to the lesion and not within it.[12,14] In these cases, the lesion may be extrabronchial and less reliably sampled. One report suggested that transbronchial needle aspiration[14] was particularly well suited to such cases, but the needle direction remains outside of the bronchoscopist's control. Newer guide sheaths also have a natural curve at the tip that may hold biopsy tool orientation towards the lesion. This gap was noted despite the application of a full range of sampling techniques (bronchial brush, transbronchial needle aspirate, transbronchial biopsy, bronchoalveolar lavage). Our study provided a signal that transbronchial needle aspiration and bronchial brushings yielded more frequent diagnostic results but no sampling technique was consistent more reliable. Our study was not powered to detect a difference between sampling instruments. There were eight procedures where a sole sampling technique was positive (Table 4) but there was no dominant instrument that improved yield. A novel sampling instrument may be beneficial. For example, a soft-tip suction catheter with sampling through the extended working channel was recently found to improve yield over standard biopsy forceps.[20] Transbronchial cryobiopsy also shows promise in evaluating peripheral lung lesions.[21,22]

Intrinsic lesion characteristics and positioning are undoubtedly an important part of the equation. The presence of an air bronchus sign on CT may be one of the more significant factors predicting success with bronchoscopic biopsy as has been demonstrated with ENB.[23] The identification of a clear airway path to a lesion on CT has also been noted to improve pEBUS diagnostic rate as compared with absence of a clear path (79% vs 0%).[15] Our study also identifies the air

bronchus sign as a predictor of failure of pEBUS alone, with ENB being required in only 13% of Tsuboi 1 & 2 lesions but 48 % of Tsuboi 3 or 'no air bronchus sign' lesions. As such, this classification may also be a predictor of when the combination pEBUS and ENB will be required.

In conclusion, current techniques such as endobronchial ultrasound and electromagnetic navigation have improved the bronchoscopist's ability to locate peripheral nodules. ENB did assist in localizing peripheral nodules when pEBUS alone was unsuccessful, but our study also demonstrated that pEBUS alone may be the only necessary technique in localizing the majority of peripheral lesions in the majority of cases. Smaller lesions and those without an air bronchus sign on CT are more likely to require ENB. There remains a gap between identifying the nodule and obtaining a diagnostic result. It is appropriate to direct attention to biopsy instrumentation and technique in order to narrow this gap.

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