—Original Article—

Impact of sedation technique on the diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle aspiration

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ABSTRACT

Background and Objectives: There is a paucity of data concerning the impact of the sedation technique used for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) on diagnostic accuracy. The aim of this retrospective study was to compare the diagnostic accuracy of EBUS-TBNA in deep and moderate sedations, and to investigate other possible determinants of diagnostic accuracy in three lymph node locations (mediastinal, subcarinal, and hilar). **Materials and Methods:** The first consecutive patients at our institution undergoing EBUS-TBNA for selective sampling in deep sedation were compared with the first consecutive patients in moderate sedation between 2006 and 2014. Diagnoses based on EBUS-TBNA were compared with those on surgical or radiological follow-up. **Results:** In a total of 232 patients, the overall diagnostic accuracy for correct diagnosis at the mediastinal, subcarinal, and hilar locations irrespective of the sedation technique was 91%, 93%, and 92%, respectively. At the three mentioned lymph node locations, overall diagnostic accuracy of EBUS-TBNA in deep sedation compared to moderate sedation was 88.5% and 95.5% ($P = 0.3$), 93.2 and 93.6% ($P = 0.9$), and 88.6 and 94.0% ($P = 0.4$), respectively. **Conclusions:** The sedation technique does not seem to influence the diagnostic accuracy of EBUS-TBNA.

Key words: Anesthesia, diagnostic accuracy, efficacy, endobronchial ultrasound (EBUS), transbronchial needle aspiration (TBNA)

INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become a standard technique for the diagnosis and staging of mediastinal and hilar lymph nodes with an excellent safety profile and overall test performance.[1-3] Diagnostic accuracy of EBUS-TBNA is higher compared to positron emission tomography (PET) and similar compared to mediastinoscopy for staging of mediastinal lymph nodes.[4-6] In patients with nonsmall cell lung cancer (NSCLC), EBUS-TBNA has been shown to reliably sample lymph nodes even with no radiological evidence of metastasis or enlargement.[7,8] Furthermore, EBUS-TBNA has a high diagnostic yield in other oncological or nononcological diagnoses such as small cell

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lung cancer (SCLC),[9] extrathoracic malignancy,[10] lymphoma,[11] sarcoidosis,[12,13] and tuberculosis.[14]

In conventional TBNA without EBUS guidance, major predictors of a successful aspirate have been identified including target size and location, experience of the bronchoscopist, needle size, final diagnosis, and the number of sampled lymph nodes.[15] In contrast, only few selected criteria influencing the diagnostic accuracy of EBUS-TBNA have been investigated that led to conflicting results.[2,16]

Bronchoscopy and EBUS-TBNA can be performed either in deep sedation (general anesthesia) or in moderate sedation (conscious sedation) with propofol or the combined administration of benzodiazepines and opiates.[17,18] However, there is a paucity of data concerning the impact of the sedation technique used for EBUS-TBNA on diagnostic accuracy. The aim of this study was to compare the diagnostic accuracy of EBUS-TBNA obtained in deep and moderate sedations, and to investigate the impact of other characteristics on diagnostic accuracy in three lymph node locations.

MATERIALS AND METHODS

Subjects and final diagnosis

Between September 2007 and January 31 2014, all consecutive patients who underwent EBUS-TBNA at our institution for selective assessment of enlarged [≥1 cm by computed tomography (CT) or ultrasound] or suspected [enhanced fluorodeoxyglucose (FDG) activity in PET/CT] lymph nodes were enrolled. Demographic and clinical data, procedural reports, and cytological findings were collected from medical records. CT or PET/CT scans were prospectively reviewed to gather the size and standard uptake value (SUV) of FDG of each sampled lymph node. The cytological findings obtained with EBUS-TBNA were verified by histological examination if a surgical biopsy (mediastinoscopy, thoracoscopy, or thoracotomy) was carried out following EBUS-TBNA or alternatively by clinical and radiological follow-up data.

The study was approved by the local ethics committee (KEK-StV-Nr. 61/13). The study is registered at ClinicalTrials.gov (Identifier: NCT02245295).

Subject allocation and sedation technique

EBUS-TBNA was performed either under general anesthesia by a thoracic surgeon or a pulmonologist (D.S., D.F., M.K.), or by one of the pulmonologists (M.K., D.F.) in moderate sedation. All three physicians who performed EBUS-TBNA for this study had a comparable experience level in EBUS bronchoscopy, making the effect of the learning curve negligible. The first 116 consecutive patients undergoing EBUS-TBNA in deep sedation were compared with the first 116 consecutive patients with EBUS-TBNA in moderate sedation. On this basis, there was a pseudorandomization to one of the groups.

Deep sedation (general anesthesia) was induced and maintained intravenously by an anesthetist administering propofol, benzodiazepines, and opiates. Airway patency and mechanical ventilation was maintained using a laryngeal mask. Moderate sedation was achieved by single-drug administration of propofol with an intermittent intravenous bolus technique by a specially trained nurse who was attending the bronchoscopist. After an initial induction dose ranging between 30 mg and 40 mg, repeated doses between 10 mg and 20 mg were given to maintain sedation. Additionally, coughing was suppressed by pharyngeal, laryngeal and tracheal application of lidocaine through the bronchoscope. All EBUS-TBNAs in moderate sedation were performed in the endoscopy unit, whereas EBUS-TBNAs in general anesthesia were performed in the operation room.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)

For EBUS-TBNA, the convex probe EBUS (BF-UC160F-OL8, Olympus, Tokyo, Japan) was used in all cases. After insertion of the EBUS bronchoscope into the trachea directly or through the laryngeal mask airway, the transducer was brought into contact with the airway mucosa and moved in all directions to identify the target lesion for sampling. Selectively, a balloon attached on the transducer was inflated with saline solution or Doppler mode imaging was applied. A 22-gauge TBNA needle equipped with a protective sheath (NA-201SX-4022, Olympus, Tokyo, Japan) was passed through the working channel of the bronchoscope. After visualization of the target lymph node, the TBNA needle was passed out of the sheath into the lymph node. After that, the internal stylet was removed and suction was applied with a dedicated syringe moving the needle forward and backward. After the sampling, the negative pressure was released and the needle was retrieved. The specimen collected in the lumen of the needle was blown out by an air-filled syringe onto a glass slide. The specimen on the

slide was smeared with another glass slide and fixed in 95% alcohol by a cytotechnologist of the Institute of Surgical Pathology of the University Hospital, Zurich, Zurich, Switzerland. The residual specimen stored in the lumen of the needle was then rinsed with 1-2 mL of sterile saline into a formalin solution for cell block analysis. Smear and cell block were transferred to the Institute of Surgical Pathology for cytological evaluation by two cytopathologists. Rapid on-site cytological evaluation (ROSE) was not performed.

Outcome measures

The main outcome was to determine and compare the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy of EBUS-TBNA obtained during two different sedation techniques (deep versus moderate sedation) in three lymph node locations (mediastinal, subcarinal, and hilar). Furthermore, in univariate and multivariate analyses, other characteristics with a possible impact on the diagnostic accuracy of EBUS-TBNA including size (short axis) and SUV of the target lymph node as well as the number of needle passes, availability of a PET/CT scan prior to EBUS-TBNA, and final diagnosis were investigated.

According to the classification of the American Thoracic Society, lymph nodes in stations 2 and 4 were defined as "mediastinal." The "subcarinal" lymph node included station 7, and stations 10, 11, and 12 were "hilar" lymph nodes. The performance characteristics (sensitivity, specificity, and overall diagnostic accuracy) of EBUS-TBNA were calculated as previously described.[19] Overall, diagnostic accuracy is the weighted average of a test's sensitivity and specificity where sensitivity is weighted by prevalence and specificity is weighted by the complement of prevalence.[19]

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22 (IBM Corporation, Armonk, NY, USA). Diagrams are designed using SigmaPlot™, version 11 (Systat Software, Inc., San Jose, CA, USA). Data are reported as median ± interquartile range (IQR), or mean ± standard deviation (SD), or percentages as appropriate. Distribution of normality was tested with the one-sample Kolmogorov-Smirnov test. Demographic, clinical, and radiological data in the two sedation groups were compared with the Pearson χ^2 test, Mann-Whitney *U* test, or Student's *t*-test as appropriate. Statistical significance of possible determinants of diagnostic accuracy was assessed using logistic regression analysis. Variables with a *P* value of equal to or less than 0.2 in the univariate analysis were entered into the multivariate model. *P* values of all outcomes were two-sided; a value less than 0.05 was considered to indicate statistical significance.

RESULTS

The first 116 consecutive patients who underwent EBUS-TBNA under moderate sedation (60.3% males had a median age of 62 years (IQR 48-71 years) compared with the first 116 consecutive patients who had their EBUS-TBNA obtained during deep sedation (62.1% males, median age 64 years, IQR 56-69 years). The demographic data of both groups are summarized in Table 1. Lymph node characteristics according to the three lymph node locations and the sedation technique are displayed in Table 2. Several baseline variables were not equally distributed between the two groups. Compared to EBUS-TBNA under moderate sedation, patients in the deep sedation group had significantly more approaches to mediastinal lymph nodes ($P = 0.001$), more PET/CT scans before bronchoscopy ($P = 0.002$), more needle passes ($P = 0.002$), and more NSCLCs as final diagnosis ($P = 0.001$). However, in all three locations, lymph node size and maximum SUV in the PET/CT were comparable.

Diagnostic accuracy

Sensitivity, specificity, NPV, PPV, and overall diagnostic accuracy of EBUS-TBNA in all patients irrespective of the sedation technique are displayed in Table 3 according to the three lymph node locations. NPV and overall diagnostic accuracy of EBUS-TBNA in the subcarinal location are slightly superior to other locations but the sensitivity was comparable in the three lymph node locations (88.0%, 88.6%, and 86.2%, respectively).

Sedation technique

In all three lymph node locations, the overall diagnostic accuracy of EBUS-TBNA obtained under deep sedation did not differ significantly from than obtained under moderate sedation [Figure 1]. At the mediastinal lymph node location, overall diagnostic accuracy of EBUS-TBNA in deep sedation and moderate sedation was 88.5 and 95.5% ($P = 0.3$), respectively. At the subcarinal and hilar locations, the corresponding diagnostic accuracies were 93.2% and 93.6% ($P = 0.9$), and 88.6% and 94.0% ($P = 0.4$), respectively. The sensitivity, specificity, and NPV between both sedation techniques

Table 1. Demographic, clinical, and x-ray characteristics of the 232 study patients

	DS (*n* = 116)	MS (*n* = 116)	*P* value*	Total (*n* = 232)
Male gender, *n* (%)	72 (62.1)	70 (60.3)	0.9	142 (62.2)
Age, median years (IQR)	64 (56-69)	62 (48-71)	0.5	63 (55-70)
PET/CT before EBUS, *n* (%)	93 (80.2)	49 (42.2)	0.0001	142 (61.2)
N of sampled Ln locations, median (IQR)	1 (1-2)	1 (1-2)	0.5	1 (1-2)
Sampled lymph node locations				
2 and 4, *n* (%)	78 (67.2)	44 (37.9)	0.0001	122 (52.6)
ATS 7, *n* (%)	44 (37.9)	79 (68.1)	0.0001	123 (53.0)
ATS 10-12, *n* (%)	36 (31.6)	50 (43.1)	0.08	86 (37.1)
Surgical confirmation, *n* (%)	63 (54.3)	19 (16.4)	0.0001	82 (35.3)
Diagnosis of malignancy, *n* (%)	106 (91.4)	78 (67.2)	0.0001	184 (79.3)
NSCLC	72 (62.1)	54 (46.6)	0.001	126 (54.3)
SCLC	4 (3.4)	9 (7.8)	0.018	13 (5.6)
Lymphoma	5 (2.6)	5 (4.3)	0.2	8 (3.4)
Extrapulmonary carcinoma	26 (22.4)	16 (13.8)	0.5	42 (18.1)
Sarcoidosis	11 (9.5)	32 (27.6)	0.001	43 (18.5)
Adverse events, *n* (%)	5 (4.3)	8 (6.9)	0.6	13 (5.6)

DS: Deep sedation, MS: Moderate sedation, PET/CT: Positron emission tomography/computed tomography, EBUS: Endobronchial ultrasound, Ln: Lymph node, NSCLC: Nonsmall cell lung cancer, SCLC: Small cell lung cancer, IQR: Interquartile range, *Fisher's exact test or Mann-Whitney *U* test, as appropriate

Table 2. Baseline lymph node characteristics

	ATS 2, 4 (*n* = 122)	ATS 7 (*n* = 123)	ATS 10-12 (*n* = 86)
Moderate sedation, *n* (%)	44 (36.1)*	79 (64.2)*	50 (58.1)
Size, median cm (IQR)	1.6 (1.2-2.0)	1.8 (1.3-2.5)	1.6 (1.2-2.2)
Needle passes, median (IQR)	5 (4-8)*	4 (3-6)	4 (3-6)*
PET/CT before EBUS, *n* (%)	87 (71.3)*	66 (53.7)*	53 (61.6)*
SUV maximum, median (IQR)	7.6 (4.3-9.4)	6.7 (4.2-10.5)	6.7 (4.4-11.0)
Additional TBNA			
ATS 2 and 4, *n* (%)	–	57 (46.3)*	25 (29.1)
ATS 7, *n* (%)	57 (46.7)*	–	36 (41.9)*
ATS 10-12, *n* (%)	25 (20.5)	36 (29.3)	–
NSCLC, *n* (%)	106 (86.9)*	88 (71.5)*	66 (76.7)

PET/CT: Positron emission tomography/computed tomography, EBUS: Endobronchial ultrasound, TBNA: Transbronchial needle aspiration, SUV: Standard uptake value, NSCLC: Nonsmall cell lung cancer, IQR: Interquartile range, *$P < 0.05$ (deep versus moderate sedation)

did not show a statistically significant difference at any lymph node location [Tables 4 and 5].

Multivariate analysis

In the multivariate analysis, the number of needle passes ($P = 0.02$) and the number of sampled lymph nodes ($P = 0.01$) were significant predictors of a successful aspirate in the subcarinal position only [Table 6]. In the mediastinal and hilar positions, this association was not significant. In all three lymph node locations, neither the sedation technique nor any of the other variables listed in Table 2 were significantly associated with an improved diagnostic accuracy of EBUS-TBNA [Table 6]. Notably, lymph node size, maximum SUV, and a PET/CT scan before bronchoscopy were not independently associated with diagnostic accuracy.

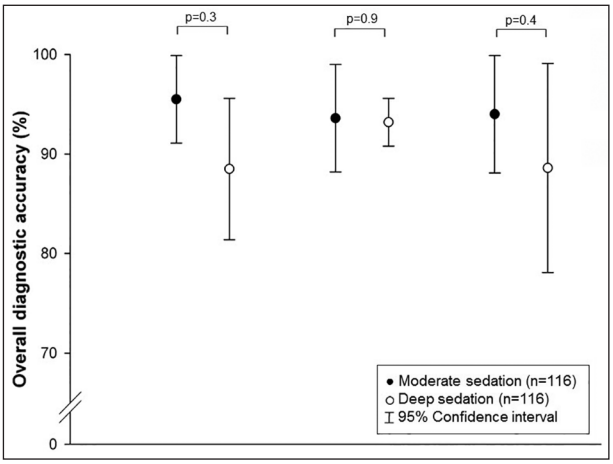

Figure 1. Overall diagnostic accuracy of EBUS-TBNA according to sedation technique

Adverse events

Adverse events after EBUS-TBNA were uncommon in the deep sedation and moderate sedation groups (4.3% and 6.9%, respectively, $P = 0.6$) and of minor severity. Most of the complications in the patients with moderate sedation were related to oxygen desaturation events or transient apnea. There was no case of a severe adverse event.

DISCUSSION

TBNA is a minimally invasive and safe technique for the first-line investigation of patients with suspected or enlarged mediastinal or hilar lymph nodes. Since

Table 3. Diagnostic accuracy of EBUS-TBNA according to lymph node location in all patients under a) moderate sedation and b) deep sedation

N = 232	ATS 2, 4 (*n* = 122)	ATS 7 (*n* = 123)	ATS 10-12 (*n* = 86)
Sensitivity	88.0 (80.0-93.9)	88.6 (78.7-94.9)	86.2 (74.6-93.8)
Specificity	100 (88.3-100)	100 (93.8-100)	100 (87.1-100)
Negative predictive value	73.2 (57.1-85.8)	86.7 (75.4-94.1)	77.1 (59.9-90.0)
Positive predictive value	100 (95.6-100)	100 (94.2-100)	100 (92.8-100)
Overall accuracy	91.0 (81.1-96.5)	93.4 (83.6-98.4)	91.8 (81.9-97.3)

Data in the table are displayed in % (95% CI)

Table 4. Diagnostic accuracy of EBUS-TBNA according to lymph node location in moderate sedation

N = 116	ATS 2, 4 (*n* = 44)	ATS 7 (*n* = 78)	ATS 10-12 (*n* = 50)
Sensitivity	93.1 (77.2-98.9)	88.1 (74.4-96.0)	87.5 (71.0-96.4)
Specificity	100 (78.0-100)	100 (90.2-100)	100 (81.3-100)
Negative predictive value	88.2 (63.5-98.2)	87.8 (78.8-95.9)	81.8 (59.7-94.7)
Positive predictive value	100 (87.1-100)	100 (90.4-100)	100 (87.5-100)
Overall accuracy	95.5 (89.4-100)	93.6 (88.2-99.0)	94.0 (87.4-100)

Data in the table are displayed in % (95% CI)

Table 5. Diagnostic accuracy of EBUS-TBNA according to lymph node location in deep sedation

N = 116	ATS 2, 4 (*n* = 78)	ATS 7 (*n* = 44)	ATS 10-12 (*n* = 35)
Sensitivity	85.7 (74.6-93.2)	89.3 (71.8-97.6)	84.6 (65.1-95.6)
Specificity	100 (78.0-100)	100 (79.2-100)	100 (66.2-100)
Negative predictive value	62.5 (40.6-81.2)	84.2 (60.4-96.4)	69.2 (38.6-90.7)
Positive predictive value	100 (93.3-100)	100 (86.2-100)	100 (84.4-100)
Overall accuracy	88.5 (81.4-95.6)	93.2 (90.8-100)	88.6 (78.1-99.1)

Data in the table are displayed in % (95% CI)

Table 6. Logistic regression analysis of variables with possible impact on diagnostic accuracy

	Univariate analysis			Multivariate analysis		
	β-coeffi-cient	SE	*P* value	β-coeffi-cient	SE	*P* value
ATS 2 and 4						
Sedation technique	1.01	0.81	0.2*	0.85	0.82	0.3
PET/CT before EBUS	0.27	0.81	0.7			
SUV maximum	−0.18	0.11	0.9			
N of sampled lymph nodes locations	0.78	0.46	0.09*	0.71	0.46	0.1
Lymph node size	−0.07	0.25	0.8			
Needle passes	0.13	0.13	0.3			
Final diagnosis	−0.09	0.23	0.7			
ATS 7						
Sedation technique	0.07	0.76	0.9			
PET/CT before EBUS	−0.12	0.76	0.9			
SUV maximum	0.29	0.23	0.3			
N of sampled lymph nodes locations	1.06	0.61	0.09*	1.76	0.70	0.012
Lymph node size	0.26	0.50	0.6			
Needle passes	0.41	0.28	0.1*	0.84	0.37	0.022
Final diagnosis	0.20	0.84	0.3			
ATS 10-12						
Sedation technique	0.70	0.80	0.4			
PET/CT before EBUS	1.10	1.28	0.6			
SUV maximum	−0.12	0.07	0.07*	−0.72	0.07	0.3
N of sampled lymph nodes locations	1.31	0.74	0.08*	0.73	0.73	0.3
Lymph node size	−0.28	0.25	0.3			
Needle passes	−0.10	0.14	0.5			
Final diagnosis	0.72	0.51	0.2*	0.70	0.63	0.3

SE: Standard error, PET/CT: Positron emission tomography/computed tomography, EBUS: Endobronchial ultrasound, TBNA: Trans-bronchial needle aspiration, SUV: Standard uptake value, Ln: Lymph node, *Independent variables with a $P \leq 0.2$ in the univariate analysis were included in the multivariate model

the widespread introduction of EBUS guidance, the diagnostic accuracy has improved considerably. In conventional TBNA without EBUS guidance, major predictors of a successful aspirate have been identified including target size and location, experience of the bronchoscopist, needle size, final diagnosis, and the number of sampled lymph nodes.[15] Determinants of diagnostic accuracy in EBUS-TBNA were addressed in three studies.[2,16,20] And there are three studies available assessing the impact of the sedation technique on diagnostic accuracy of EBUS-TBNA but with conflicting results. Whereas one prospective, randomized trial performed by Casal *et al.* and one retrospective study performed by Cetinkaya *et al.* found no difference in yield based on the use of moderate or deep sedation,[20,21] the other study performed by Yarmus *et al.* reported a higher yield for procedures in general anesthesia.[22] However, in the latter study significantly more lymph nodes were sampled per patient in the deep sedation group, which probably enhances the chance of a successful aspirate and confounds this finding. On the other hand, a very recent prospective study confirmed that EBUS-TBNA under light-conscious sedation is not only well-tolerated but also comparable concerning its diagnostic performance in deep sedation.[18] In our study, there was no significant difference in diagnostic accuracy between both sedation techniques although more lymph nodes per patient were sampled in the deep sedation group. Moreover, in the multivariate analysis we identified the number of sampled lymph nodes and number of needle passes as significant predictors of a successful aspirate in the subcarinal lymph node location, which is an inconsistent finding in other studies.[2,15,20] However, in the review published by Bonifazi *et al.*, only conventional TBNA without the use of EBUS were considered.[15] In our study, the association of improved diagnostic accuracy and the number of needle passes was not significant in other than the subcarinal lymph node location. Moreover, we were not able to identify any other factor independently influencing the probability of a true-positive or true-negative result of EBUS-TBNA irrespective of the lymph node location. The lymph node size was particularly not associated with an improved diagnostic accuracy when only lymph nodes greater than 1 cm were sampled. This finding is supported by two studies showing no significant association between diagnostic accuracy and nodal size.[2,20] Contrarily, the sensitivity and specificity decreased with small nodal size in the retrospective study by Kennedy *et al.*[16] Nevertheless, we agree with Herth *et al.* stating that EBUS-TBNA can accurately sample even small mediastinal lymph nodes.[7] However, in their study, EBUS-TBNA was performed in deep sedation only. According to our data, this is also true for EBUS-TBNA obtained in moderate sedation.

Contrary to the findings of others[3,23] there was no evidence of improved diagnostic accuracy in FDG-PET/CT positive lymph nodes. Furthermore, we were not able to detect a significant influence of the final diagnosis on diagnostic accuracy. For NSCLC, SCLC, tuberculosis, and sarcoidosis, there were comparable diagnostic accuracies of EBUS-TBNA in our study, which was in line with the findings of a previous study.[24] The sensitivity and diagnostic accuracy of EBUS-TBNA for the diagnosis of neoplastic disease in the latter study were 87% (95% CI, 77-97%) and 95% (95% CI, 91-99%), respectively, and for the diagnosis of sarcoidosis, the sensitivity and diagnostic accuracy were 83% (95% CI, 69-97%) and 96% (95% CI, 93-99%) respectively.[24]

The reported overall sensitivity, NPV, and diagnostic accuracy of EBUS-TBNA irrespective of the lymph node location had a range of 83-97%, 73-99%, and 90-98%, respectively.[2,4,9,10,12,13,24] According to meta-analysis data, the pooled sensitivity of EBUS-TBNA of the mediastinal lymph nodes is 88% (95% CI 79 to 94%),[1] which is in line with our own results. Compared to the sensitivity in mediastinal lymph nodes with range 81-95%, [1, 3, 5-8, 11, 16] the reported sensitivity in the hilar location is slightly inferior with 76-91%.[23,25] However, in a retrospective study performed by Kennedy *et al.*, the lymph node location did not significantly influence the results of EBUS-TBNA.[16] Accordingly, EBUS-TBNA has been recently shown to accurately access the hilar and interlobar lymph nodes in patients with potentially resectable lung cancer with a diagnostic accuracy of 96.6%.[25] These findings are supported by our own data suggesting a comparable diagnostic accuracy in mediastinal (91.0-93.4%) and hilar lymph nodes (91.8%).

There are some limitations in this study, which are mainly due to its retrospective design. Some bias concerning patient allocation is inevitable although the decision as to whether an EBUS-TBNA was performed under moderate sedation or deep sedation was most often made by chance, mainly depending on the fact of whether the patient was referred to the Division of Pulmonology or the Division of Thoracic Surgery.

Anyway, this fact may lend a pseudorandomization to this study. However, the thoracic surgeons performed EBUS-TBNA only under general anesthesia, whereas pulmonologists tended to perform more EBUS-TBNA under moderate sedation. Unfortunately, the recording of procedure durations was only available for patients undergoing EBUS-TBNA under general anesthesia. However, we believe that procedure duration for EBUS-TBNA exclusively may be shorter in general anesthesia compared to moderate sedation. Considering the preparations and recovery time of general anesthesia, this effect is probably waning.

Finally, there are some general caveats when interpreting studies of diagnostic accuracy since they are known to report heterogeneous and incomplete outcomes. As observed in other studies, conclusions from published data are limited by sample size and particularly, alternative definitions of diagnostic accuracy and diagnostic yield. Overall accuracy harbors the intuitive appeal as a single measure of test validity; however, dependence on prevalence renders it inferior to the consideration of sensitivity and specificity.[19] Nevertheless, we have chosen to present overall diagnostic accuracy data beside sensitivity, specificity, PPV and NPV because most of the studies investigating the diagnostic utility of EBUS-TBNA report its accuracy. In fact, in the majority of the studies it is not clear whether diagnostic yield or accuracy was presumed. We feel that reporting overall diagnostic accuracy considers the true-negative ratio and true-positive ratio in one value.

CONCLUSION

In conclusion, the sedation technique does not seem to influence the diagnostic accuracy of EBUS-TBNA. Instead, we identified the number of sampled lymph nodes and the number of needle passes as significant predictors of a successful aspirate in the subcarinal lymph node location.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Adams K, Shah PL, Edmonds L, *et al*. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: Systematic review and meta-analysis. *Thorax* 2009;64:757-62.
2. Ye T, Hu H, Luo X, *et al*. The role of endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) for qualitative diagnosis of mediastinal and hilar lymphadenopathy: A prospective analysis. *BMC Cancer* 2011;11:100.
3. Gu P, Zhao YZ, Jiang LY, *et al*. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: A systematic review and meta-analysis. *Eur J Cancer* 2009;45:1389-96.
4. Yasufuku K, Nakajima T, Motoori K, *et al*. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest* 2006;130:710-8.
5. Yasufuku K, Pierre A, Darling G, *et al*. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. *J Thorac Cardiovasc Surg* 2011;142:1393-400.e1.
6. Annema JT, van Meerbeeck JP, Rintoul RC, *et al*. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: A randomized trial. *JAMA* 2010;304:2245-52.
7. Herth FJ, Ernst A, Eberhardt R, *et al*. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. *Eur Respir J* 2006;28:910-4.
8. Herth FJ, Eberhardt R, Krasnik M, *et al*. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal mediastinum in patients with lung cancer. *Chest* 2008;133:887-91.
9. Wada H, Nakajima T, Yasufuku K, *et al*. Lymph node staging by endobronchial ultrasound-guided transbronchial needle aspiration in patients with small cell lung cancer. *Ann Thorac Surg* 2010;90:229-34.
10. Navani N, Nankivell M, Woolhouse I, *et al*. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy: A multicenter study. *J Thorac Oncol* 2011;6:1505-9.
11. Kennedy MP, Jimenez CA, Bruzzi JF, *et al*. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. *Thorax* 2008;63:360-5.
12. Tremblay A, Stather DR, Maceachern P, *et al*. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. *Chest* 2009;136:340-6.
13. Oki M, Saka H, Kitagawa C, *et al*. Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis. *J Thorac Cardiovasc Surg* 2012;143:1324-9.
14. Sun J, Teng J, Yang H, *et al*. Endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing intrathoracic tuberculosis. *Ann Thorac Surg* 2013;96:2021-7.
15. Bonifazi M, Zuccatosta L, Trisolini R, *et al*. Transbronchial needle aspiration: A systematic review on predictors of a successful aspirate. *Respiration* 2013;86:123-34.
16. Kennedy MP, Jimenez CA, Morice RC, *et al*. Factors influencing the diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration. *J Bronchology Interv Pulmonol* 2010;17:202-8.
17. Wahidi MM, Jain P, Jantz M, *et al*. American College of Chest Physicians consensus statement on the use of topical anesthesia, analgesia, and sedation during flexible bronchoscopy in adult patients. *Chest* 2011;140:1342-50.

18. Jeyabalan A, Medford AR. Endobronchial ultrasound-guided transbronchial needle aspiration: Patient satisfaction under light conscious sedation. *Respiration* 2014;88:244-50.
19. Alberg AJ, Park JW, Hager BW, *et al*. The use of "overall accuracy" to evaluate the validity of screening or diagnostic tests. *J Gen Intern Med* 2004;19:460-5.
20. Cetinkaya E, Ozgül MA, Tutar N, *et al*. The diagnostic utility of real-time EBUS-TBNA for Hilar and mediastinal lymph nodes in conventional TBNA negative patients. *Ann Thorac Cardiovasc Surg* 2014;20:106-12.
21. Casal RF, Lazarus DR, Kuhl K, *et al*. Randomized Trial of endobronchial ultrasound-guided transbronchial needle aspiration under general anesthesia versus moderate sedation. *Am J Respir Crit Care Med* 2015;191:796-803.
22. Yarmus LB, Akulian JA, Gilbert C, *et al*. Comparison of moderate versus deep sedation for endobronchial ultrasound transbronchial needle aspiration. *Ann Am Thorac Soc* 2013;10:121-6.
23. Ernst A, Eberhardt R, Krasnik M, *et al*. Efficacy of endobronchial ultrasound-guided transbronchial needle aspiration of hilar lymph nodes for diagnosing and staging cancer. *J Thorac Oncol* 2009;4: 947-50.
24. Gindesgaard CB, Schousboe LP, Christensen RK. Endobronchial ultrasound-guided transbronchial needle aspiration in an unselected cohort. *J Bronchology Interv Pulmonol* 2013;20:140-6.
25. Yasufuku K, Nakajima T, Waddell T, *et al*. Endobronchial ultrasound-guided transbronchial needle aspiration for differentiating N0 versus N1 lung cancer. *Ann Thorac Surg* 2013;96:1756-60.