Research Article
Open Access

Predictors of actionable results in endobronchial ultrasound-guided transbronchial needle aspiration

Abstract

Objectives: Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technique for obtaining tissue samples from mediastinum. Factors associated with actionability (subsequent management resulting from identification of diagnostic tissues in EBUS-TBNA) including utility of a rapid on-site evaluation (ROSE) are not clearly determined. The objective of this study is to determine predictors of actionability after EBUS-TBNA.

Methods: A chart review of patients undergoing EBUS-TBNA was performed. A multivariate model was used to determine the predictors of actionability. An a-priori sub-analysis was also performed to compare the association of ROSE with respect to final pathology and actionability.

Results: 191patients with a mean age of 61.5±15.0years underwent EBUS-TBNA. Multivariate analysis revealed ROSE positive cytology (ROSE(+), adequate diagnostic tissues determined by cytotechnician) as the sole predictor of actionability with an odds ratio of 228.3, p=0.0007. Sub-analysis of the utility of ROSE showed that having a ROSE(+) compared to a ROSE negative cytology (ROSE(-), inadequate diagnostic tissues determined by cytotechnician) was associated with superior proportion of actionability (ROSE(+):153(87.9%) versus ROSE(-):1(5.9%), p<0.0001). Furthermore, proportion of positive pathology (adequate diagnostictissues as determined by a pathologist) (ROSE(+):158(90.8%) versus ROSE(-):3(17.7%), p<0.0001)) and diagnostic pathology (pathological diagnosis of benign or malignant) (ROSE(+): 158 (90.8%) versus ROSE(-):2(11.8%),p<0.0001)) were higher in the cohort with ROSE(+) cytology.

Conclusion: A ROSE(+) is a strong predictor of actionability and is associated with a greater diagnostic yield. The cytotechnicians performing ROSE have a positive impact on the outcome of EBUS-TBNA and therefore increase the quality of care for patients with mediastinal pathology.

Keywords: lung cancer, mediastinal, hilar lymph nodes, ebus, lymph node pathology, cancer diagnostic testing

Volume 3 Issue 3 - 2016

Muneeb Mohammed,[1] Saswata Deb,[1] Kamiyar Soghrati,[2] Abdollah Behzadi[1,2]

[1]Department of Thoracic Surgery, University of Toronto, Canada
[2]Department of Respirology, University of Toronto, Canada

Correspondence: Abdollah Behzadi, Department of Thoracic Surgery, University of Toronto, Canada, 2200 Eglinton Avenue West Suite 4F417, Mississauga, ON L5M 2N1, Canada, Tel 905-813-1100, Fax 905-813-4024,
Email Abdollah.Behzadi@trilliumhealthpartners.ca

Received: August 01, 2016 | **Published:** August 16, 2016

Abbreviations: EBUS-TBNA, endobronchial ultrasound guided transbronchial needle aspiration;

ROSE, rapid onsite evaluation; Ct, computed tomography

Introduction

Endobronchial ultrasound-guided needle aspiration (EBUS-TBNA) is a minimally invasive and cost-effective technique to obtain tissue material from mediastinal and hilar lymph nodes and masses.[1,2] It allows the operator to perform tissue biopsies using real-time sonographic image.[2,3] EBUS-TBNA plays an important role in evaluation of peribronchial lymphadenopathy, endobronchial abnormalities, and in diagnosis of lung cancers, lymphomas, tuberculosis, and sarcoidosis.[4,5] Several studies have reported high sensitivities (70-96%) and high specificities (95-100%) with less than 1% chance of complications and no associated mortalities.[6] Thus, making EBUS-TBNA a valuable alternative to mediastinoscopy especially for benign conditions and early cancer staging.[4,7]

Biopsied material undergoes rapid onsite evaluation (ROSE) by a cytopathology technician to provide immediate feedback to the EBUS operator in the endoscopy suite.[8] The use of ROSE has shown to lower the number sites biopsied and the amount of tissue to be assessed by cytopathologist, thereby lowering costs and improving efficiency of EBUS-TBNA.[9–11]

"Action ability" is a concept that deals with the ability to make a decision regarding a patient's medical management. An actionable result is therefore a result that guides the decision towards treatment or no treatment. Actionable result in EBUS-TBNA includes diagnosis of malignancy or benign which would enable the physician to initiate the appropriate treatment option. A non-actionable result is non-diagnostic and provides no new information requiring an additional diagnostic test for patient management. Therefore, non-actionable EBUS-TBNA procedures are often followed up with another diagnostic procedure such as mediastinoscopy. The objective of the study is to determine predictors of action ability in EBUS-TBNA and to analyze ROSE and therefore the impact of cytotechnicians on the outcome of EBUS-TBNA.

Material and methods

We conducted a single centered retrospective study at a community hospital. Research Ethics Board approval was received before initiating

the study. We retrospectively studied EBUS-TBNA procedures performed on patients with intrathoracic lymphadenopathy from April 2013 to May 2015. The study included all patients who underwent the EBUS-TBNA procedure at our institution and had adequate medical records to determine the outcome from the procedure. Patients with incomplete medical records were excluded from the study. From the two-year time period, 191cases were included in the study.

All patients had a computed tomography (CT) scan prior to their EBUS-TBNA procedure. Some patients who were suspected to have a malignant condition underwent additional radiological investigations such as positron emission tomography and/or bone scans.

All EBUS-TBNA were performed between two thoracic surgeons and three respirologists. Patients about to undergo the procedure would be brought into the endoscopy suite and given intravenous general anesthesia as well as local lidocaine sedation. After the patient was adequately sedated with minimal gag reflex, an initial airway examination would be done using the flexible bronchoscope and secretions suctioned. The bronchoscope was then retracted and the EBUS bronchoscope was introduced. The operator would then view ultrasonographic and bronchoscopic images before choosing a biopsy target. Next, a transbronchial needle, of either 21 or 22 gauge, would be advanced through a working channel in the EBUS bronchoscope. Multiple passes from each site would be taken to ensure adequate tissue sample. The cytotechnologist present would perform a rapid onsite evaluation (ROSE) of the sample and indicate if diagnostic material was obtained. The EBUS operator would decide on the number of biopsies to perform and the site(s) to biopsy based on the information from the cytotechnicians. The EBUS-TBNA procedure was completed after enough samples were obtained. The patient was then sent to the recovery room for monitoring until they recovered from their sedation. A cytopathologist would then later review the biopsy material and provide a pathological diagnosis when possible. Patients were then followed up within a week with the results of EBUS-TBNA and managed accordingly.

A list of patients who had undergone EBUS-TBNA during the study time period was generated at the endoscopy clinic. Using the electronic medical records system, patient data was collected in a secure workbook. Patient information was de-identified by assigning a random alpha-numeric ID in place of patients' names.

The main objective of the study was to identify the predictors for actionability or diagnostic yield for EBUS-TBNA. Number of biopsies, node size in short axis, needle size, accessibility of the node stations, number of stations biopsied, and the type of EBUS operator (surgeon vs respirologist) were the categories analyzed for predicting actionability. The second objective was to determine the importance of cytotechnicians in EBUS-TBNA by assessing ROSE. ROSE was compared with cytopathology, actionability, pathological diagnosis, and clinical diagnosis.

Data analysis

We compared twelve variables of EBUS-TBNA in a multivariate model to determine predictors of action ability: age, sex, node size, number of biopsies, needle size, stations accessibility, Number of stations, year EBUS-TBNA performed, type of operator (surgeon vs respirologists), Operator volume and ROSE. Univariate analyses of ROSE as the variable was also done for several outcomes: action ability, lymph node pathology, diagnostic pathology, benign final Diagnosis, and malignant final diagnosis. This was done to determine accuracy and ultimately the important of ROSE in EBUS-TBNA procedures.

The chi-squared test and the *t* test were used to determine the *p* value for comparing categorical and continuous variables, respectively. A *p* value less than 0.05 was considered to be of significance. Odds ratio estimates were used to determine the 95% confidence intervals and the point estimates. For statistical analyses, we used Statistical Analysis System (SAS). Over a two-year period, 191patients who underwent EBUS-TBNA were included in this study. Table 1 summarizes the characteristics of the patients studied. There was close to an equal split between male and female patients in this study. 63.4% of the cases were performed between three respirologists and 36.6% were done between two thoracic surgeons. Of the total cases 95 received a malignant final diagnosis and 96 received a benign diagnosis. Adenocarcinoma was the most common type of malignancy and sarcoidosis was the most common benign diagnosis among the patient population.

Table 1 Predictors of actionability -multivariate model

Predictor variable	Odds ratio(Confidence Interval)	*p* Value
Age	1.0(0.97–1.06)	0.51
Female	0.8(0.25–2.85)	0.78
Operator Volume	1.0(0.98–1.05)	0.53
Node Size	0.9(0.56–1.35)	0.53
Number of Biopsies	1.0(0.64–1.48)	0.89
Needle Size	0.6(0.16–2.26)	0.45
Station Accessibility	2.1(0.21–22.15)	0.52
Number of Stations	0.7(0.11–4.80)	0.72
Year–2013 VS 2015	0.2(0.01–2.89)	0.34
Year–2014 VS 2015	0.1(0.01–1.96)	0.34
Surgeon	0.4(0.09–1.44)	0.14
ROSE	228.3(9.99–>100)	0.0007

Operator Volume, number of EBUS-TBNA procedures performed by each operator during the study period.
Node Size, short axis size(in cm) of the node biopsied as noted on the CT.
Number of Biopsies, number of total biopsies performed in a single EBUS-TBNA procedure.
Station Accessibility, lymph node stations categorized based on ease of access for TBNA.
Number of Stations, total number of stations biopsied in a single EBUS-TBNA procedure.
Year, the year the EBUS-TBNA was performed; compared previous years with current year.
Surgeon, profession of the EBUS-TBNA operator.
ROSE, rapid on-site evaluation of the TBNA by cytopathologist.
Actionable, subsequent management resulting from identification of diagnostic tissues in EBUS-TBNA.

Comparison of ROSE, final pathology and actionability in raw percentages are shown in Figure 1. Of the 191 EBUS-TBNA cases, 91.1% had positive ROSE, 83.8% had diagnostic final pathology but only 80.6% were actionable. Results from a multivariate model to determine predictors of actionability are shown in Table 1. Of the twelve variables analyzed as part of the model, ROSE was the only significant and predictor of the success of the EBUS-TBNA with a p value of 0.0007 and an odds ratio of 228.3.

Table 2 represents the different outcomes, and their significance, when the ROSE is either positive or negative. For all actionable results (total of 154), 153 were from positive ROSE and only 1 was

from negative ROSE (p value<0.0001). A positive ROSE result had strong correlation with positive and diagnostic pathology. 158 of 174 positive ROSE had diagnostic pathology with a *p* value of<0.0001.

Table 2 Onsite cytology-uni variate model

Outcomes	Positive ROSE	Negative ROSE	*p* Value
Actionable	153/174(87.9%)	1/17(5.9%)	<0.0001
Diagnostic Pathology	158/174(90.8%)	2/17(11.8%)	<0.0001
Benign Final Clinical Diagnosis	86/174(49.4%)	10/17(58.8%)	0.46
Malignant Final Clinical Diagnosis	88/174(50.6%)	7/17(41.2%)	0.46

ROSE, rapid on-site evaluation of the TBNA by cytopathologist.
Actionable, subsequent management resulting from identification of diagnostic tissues in EBUS-TBNA
Diagnostic Pathology, diagnosis of either benign or malignant by a pathologist.
Final Clinical Diagnosis, final diagnosis of benign or malignant based on tissue diagnosis(EBUS-TBNA, mediastinoscopy, or percutaneous biopsies) as well as clinical and radiological evidence.

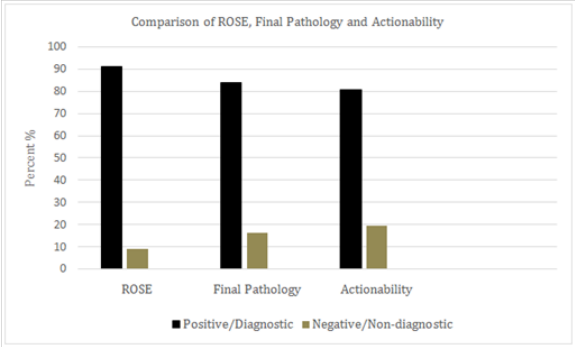

Figure 1 Percentage of ROSE, final pathology and actionability.
Definitions (Detailed Definitions at the End of Results Section):
ROSE, Rapid on-site evaluation of the TBNA by cytopathologist.
Actionable: Subsequent management resulting from identification of diagnostic tissues in EBUS-TBNA.

Detailed definitions

Age: Age of patients at the time of EBUS-TBNA procedure.

Female: Gender as recorded on the charts. Analyzed likelihood of female gender being a predictor.

Operator: Categorized by the profession of the endoscopist who performed the EBUS-TBNA. EBUS-TBNA procedures in this study were done by either a thoracic surgeon or a respirologist.

Malignant: Type of final malignant diagnosis given to the patient based on tissue diagnosis (EBUS-TBNA, mediastinoscopy, or percutaneous biopsies) as well as clinical and radiological evidence.

Benign: Type of final benign diagnosis given to the patient based on tissue diagnosis (EBUS-TBNA, mediastinoscopy, or percutaneous biopsies) as well as clinical and radiological evidence.

Number of procedures: The total number of EBUS-TBNA procedures performed by three respirologists and two thoracic surgeons over the study period of 2years.

Operator volume: Number of EBUS-TBNA procedures performed by each operator during the study period.

Node size: Short axis size (in cm) of the node biopsied as noted on the CT. If two nodes were biopsied, the size recorded was of the largest node sampled during the EBUS-TBNA procedure.

Number of biopsies: Number of total biopsies performed in a single EBUS-TBNA procedure. This is the number of times the biopsy needle was passed to the cytopathology technician. Number of biopsies is not the same as the number of passes (number of times the needle was passed in and out of a targeted node before analyzing the tissue obtained); number of passes was not recorded in most EBUS-TBNA reports and therefore could not be used as a part of the study.

Needle size: Size of the needle used to perform the TBNA.

Station accessibility: Ease of access to the lymph nodes on EBUS-TBNA. The stations are categories based on their accessibility for biopsy during the EBUS-TBNA procedure. The stations were put into two categories. The first includes the lower numbered stations from 2 up to, and including, station 7. The second category includes all station numbers higher than 7 (not including 7). In a few cases (seven cases), there were a combination of both these categories. Here, a bias was given towards the higher numbered station and these combinations were recorded under the second category.

Number of stations: Total number of stations biopsied in a single EBUS-TBNA setting.

Year: The year the EBUS-TBNA was performed in compared to the latest EBUS procedures.

Surgeon: Categorized based on the profession of the endoscopist. Likelihood of surgeons compared to respirologists as predictors was analyzed.

ROSE: Rapid on-site evaluation of the biopsy tissue to determine if adequate lymph node material was obtained from TBNA. It was reported as negative when the onsite technician determined that adequate lymph node material for a diagnosis was not present in the biopsy material. A positive result was when the technician found adequate lymph node tissue in the biopsy material.

Actionability: An "actionable" result is a diagnosis of either malignancy or benign based on EBUS-TBNA. The result is actionable when it does not require any further diagnostic tests, such as mediastinoscopy or percutaneous biopsy, to determine the cause of lymphadenopathy. A diagnosis of malignancy is actionable because it requires an "action" in terms of treatment, such as chemotherapy or radiation therapy. A benign diagnosis is also actionable because it requires an "action" in terms of radiological follow up or no treatment. No treatment is still considered to be an "action" because it is a decision made by the physician based on the EBUS-TBNA result. The result is considered to be "non-actionable" when additional diagnostic tests had to be performed after EBUS-TBNA to determine the cause of lymphadenopathy.

Diagnostic pathology: Diagnostic pathology is when the pathologist made a diagnosis of either benign or malignant based on the biopsy tissue.

Benign final clinical diagnosis: Final diagnosis of benign given to the patient based on clinical evidence, radiological evidence and tissue pathology. Tissue pathology was obtained from EBUS-TBNA, mediastinoscopy, percutaneous biopsy, or thoracoscopic surgery. Radiologic evidence includes CT, PET or MRI.

Malignant final clinical diagnosis: Final diagnosis of malignant given to the patient based on clinical evidence, radiological evidence and tissue pathology. Tissue pathology was obtained from EBUS-TBNA, mediastinoscopy, percutaneous biopsy, or thoracoscopic surgery. Radiologic evidence includes CT, PET or MRI.

Discussion

The EBUS-TBNA cases were performed between three respirologists and two thoracic surgeons at the study's institution. As indicated in Table 3, thoracic surgeons performed 36.6% of the total cases that were included in the study. All of these cases had ROSE performed by cytotechnicians present in the endoscopy suite during the procedure.

Table 3 Baseline characteristics of the study population

Characteristics	N = 191
n	191
Age: mean±standard deviation	61.5±15.0years
Sex: *n*(percentage)	
Male	94(49.2%)
Female	97(50.8%)
Operator: *n*(percentage)	
Respirologist	121(63.4%)
Surgeon	70(36.6%)
Malignant: *n*(percentage)	95(49.7%)
Adenocarcinoma	36(37.9%)
Squamous Cell Carcinoma	19(20.0%)
Large Cell Carcinoma	3(3.2%)
Non-Small Cell of Unknown Subtype	7(7.4%)
Small Cell Carcinoma	15(15.8%)
Metastasis	4(4.2%)
Thyroid Cancer	1(1.0%)
Malignant Lymphoma	5(5.3%)
Thymic Carcinoma	1(1.0%)
Neuroendocrine Carcinoma	1(1/0%)
Unknown Malignancy	3(3.2%)
Benign: *n*(percentage)	96(50.3%)
Normal Lymph Node	22(22.9%)
Cyst	1(1.0%)
Sarcoidosis	47(49.0%)
Reactive	20(20.8%)
Benign Thyroid	2(2.1%)
Fibrosis	2(2.1%)
Tuberculosis	2(2.1%)

Operator, profession of the endoscopist who performed the EBUS-TBNA.

Malignant, final diagnosis of malignancy based on tissue diagnosis(EBUS-TBNA, mediastinoscopy, or percutaneous biopsies) as well as clinical and radiological evidence.

Benign, final diagnosis of benign based on tissue diagnosis(EBUS-TBNA, mediastinoscopy, or percutaneous biopsies) as well as clinical and radiological evidence.

Figure 1 indicates that majority of the EBUS-TBNA cases were ROSE positive (91.1%), but there was a drop in the total diagnostic pathology cases (83.8%). The actionability was further reduced at 80.6% of the cases being actionable overall. The reason majority of the EBUS-TBNA cases were ROSE positive is because the operator would attempt additional biopsies based on the feedback from the cytotechnician. If the biopsies were ROSE negative, it would indicate that the operator had missed the target and the operator would attempt another biopsy. The drop between ROSE positive and final pathological diagnosis happened when the pathologist felt that there was no enough tissue material to make an affirmative diagnosis. Therefore, requiring additional diagnostic procedures to evaluate the patients' mediastinal pathology. The reason actionability is lower than the diagnostic pathology is because in a few cases the physician did not accept the pathological diagnosis from EBUS-TBNA. In these cases, the patients had received a benign pathological diagnosis but the physician felt that this diagnosis was not consistent with the patients' clinical picture. Therefore, they required additional diagnostic testing and by definition these cases would be considered non-actionable.

Based on a multivariate analysis model, ROSE was the only significant predictor of actionable results in EBUS-TBNA. Variables such as the type of operator, needle size, node size, number of biopsies, and station accessibility did not show significance as predictors. Further analysis of ROSE revealed that it was a good indicator for action ability and diagnostic pathology.

Studies have shown that use of ROSE in EBUS-TBNA results in a fewer number of biopsies without compromising diagnostic accuracy, saving healthcare resources and lowering associated risk.[9–12] Cardoso et al.[13] in a prospective observational study stated that ROSE appeared to increase diagnostic yield and sample adequacy, but failed to provide statistical significance. An early study concluded that ROSE not only showed diagnostic benefits but leads to quicker patient management based on its rapid results.[14] Numerous studies have challenged the benefit of ROSE by stating that there is no significant improvement in diagnostic yield.[9,12,15] Yarmus et al.[16] in a randomized controlled trial demonstrated that routine use of ROSE does not result in reduced procedural time and suggested ROSE to be used in patients with likely malignant etiology and those at high procedural risk.[16]

The cytotechnologists who perform the ROSE have a significant impact on the outcome of EBUS-TBNA. Their value added is in direct relation with that of ROSE. A cytotechnician improves the success of EBUS-TBNA by increasing the action ability of the procedure and thereby improving patient care. The investment made by an institution to have a cytotechnician present during the EBUS-TBNA procedure is justified by the high likelihood of having a successful outcome. Therefore, having cytotechnicians not only improve diagnostic efficiency but also improve the quality of care provided to the patients.

Limitations

There were several assumptions made in this study which would add to its limitations. EBUS-TBNA procedures were performed by several operators and over a 2-year study period. We assumed that the operators were consistent and equally skilled in their technique and their performance. Similarly, the expertise of the on-site cytotechnician was assumed to be consistent. When multiple nodes of different sizes were biopsied, the short-axis size of the largest node was recorded. The number of passes made in each aspiration was not recorded in the medical records and thus could not be studied.

Conclusion

EBUS-TBNA is a successful minimally invasive procedure used

to obtain intrathoracic tissue samples. Among the several variables analyzed, ROSE was the only significant and strong predictor of actionable results in EBUS-TBNA. It was a strong indicator for diagnostic pathology. Cytotechnicians who perform the ROSE are an essential component and add value to make EBUS-TBNA successful. Further studies, perhaps multi-centered, are required to corroborate our findings.

Acknowledgements

The authors would like to acknowledge Shelley Barker in her assistance in generating the list of patients who underwent EBUS-TBNA at the study's institution.

We would also like to thank the Comprehensive Research Experience for Medical Students (CREMS) program for providing a research grant to enable this research study.

Conflict of interest

The author declares no conflict of interest.

References

1. Aziz F. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a concise review. *Trans Lung Cancer Res*. 2012;1(3):208–213.
2. Yasufuku K, Chiyo M, Sekine Y, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. *Chest*. 2004;126(1):122–128.
3. Wang L, Wu W, Hu Y, et al. Sonographic features of endobronchial ultrasonography predict intrathoracic lymph node metastasis in lung cancer patients. *Ann Thorac Surg*. 2015;100(4):1203–1209.
4. Jalil B, Yasufuku K, Khan A. Uses, limitations, and complications of endobronchial ultrasound. *Proc (Bayl Univ Med Cent)*. 2015;28(3):325–330.
5. Kiral N, Caglayan B, Salepci B, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing intrathoracic tuberculous lymphadenitis. *Med Ultrason*. 2015;17(3):333–338.
6. Monaco SE. Endobronchial unltrasound-guided transbronchial needle aspiration (EBUS-TBNA): a practical approach. In: Monaco SE, et al. editors. *Indications and Diagnostic Performance of EBUS-TBNA*. Switzerland: Karger; 2014. p. 29–31.
7. 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(3):710–718.
8. Bott MJ, James B, Collins BT, et al. A prospective clinical trial of telecytopathology for rapid interpretation of specimens obtained during endobronchial ultrasound-fine needle aspiration. *Ann Thorac Surg*. 2015;100(1):201–206.
9. Trisolini R, Cancellieri A, Tinelli C, et al. Rapid on-site evaluation of transbronchial aspirates in the diagnosis of hilar and mediastinal adenopathy: a randomized trial. *Chest*. 2011;139(2):395–401.
10. Baram D, Garcia RB, Richman PS. Impact of rapid on-site cytologic evaluation during transbronchial needle aspiration. *Chest*. 2005;128(2):869–875.
11. Collins BT, Chen AC, Wang JF, et al. Improved laboratory resource utilization and patient care with the use of rapid on-site evaluation for endobronchial ultrasound fine-needle aspiration biopsy. *Cancer Cytopathol*. 2013;121(10):544–551.
12. Oki M, Saka H, Kitagawa C, et al. Rapid on-site cytologic evaluation during endobronchial ultrasound-guided transbronchial needle aspiration for diagnosing lung cancer: a randomized study. *Respiration*. 2013;85(6):486–492.
13. Cardoso AV, Neves I, Magalhaes A, et al. The value of rapid on-site evaluation during EBUS-TBNA. *Rev Port Pneumol*. 2015;21(5):253–258.
14. Diacon AH, Schuurmans MM, Theron J, et al. Utility of rapid on-site evaluation of transbronchial needle aspirates. *Respiration*. 2005;72(2):182–188.
15. Griffin AC, Schwartz LE, Baloch ZW. Utility of on-site evaluation of endobronchial ultrasound-guided transbronchial needle aspiration specimens. *Cytojournal*. 2011;8:20.
16. Yarmus L, Van der Kloot T, Lechtzin N, et al. A randomized prospective trial of the utility of rapid on-site evaluation of transbronchial needle aspirate specimens. *J Bronchology Interv Pulmonol*. 2011;18(2):121–127.