

The utility of endobronchial ultrasound-transbronchial needle aspiration in lymphoma

Fayez Kheir, Ahmad Itani, Omar Assasa, Abdul Hamid Alraiyes[†]

Department of Pulmonary Diseases, Critical Care and Environmental Medicine, Tulane University Health Sciences Center, New Orleans, Louisiana, [†]Department of Medicine, Interventional Pulmonology, Roswell Park Cancer Institute, Buffalo, New York, USA

ABSTRACT

Background and Objectives: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive procedure that has a well-established role in the diagnosis and staging of lung cancer. This technology is also widely used for the diagnosis of mediastinal masses and cysts as well as other inflammatory disorders such as sarcoidosis. However, the utility of this procedure in the diagnosis and subclassification of lymphoproliferative disorders (LPDs) is not clear. We performed a systematic review to evaluate EBUS-TBNA use in LPDs. **Materials and Methods:** PubMed, EMBASE, MEDLINE, Cochrane Library Plus, and ISI Web of Knowledge were searched for studies of clinical trials in English reporting diagnostic performance of EBUS-TBNA in lymphoma until September 2014. The overall sensitivity, negative predictive value (NPV), and diagnostic accuracy were evaluated. **Results:** Six trials involving 346 patients with suspected lymphoma were included. The overall sensitivity, NPV, and diagnostic accuracy ranged 38%-91%, 83%-96.4%, and 91%-97%, respectively. Further invasive surgery was needed only in 13-43% of the patients. None of the studies included in the present review reported important complications. **Conclusion:** Current evidence suggests that EBUS-TBNA can be used as an initial evaluation for patients with suspected lymphoma. Additional surgical procedures may be necessary if a sample is inadequate or negative with high suspicion of lymphoma. Further multicenter trials are needed to evaluate the diagnostic yield of EBUS-TBNA in lymphoma patients.

Key words: Endobronchial ultrasound (EBUS), lymphoma, mediastinal lymph nodes, transbronchial needle aspiration (TBNA)

INTRODUCTION

The role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis and staging of non-small cell lung cancer has been well established as the first modality of choice. The overall sensitivity and the negative predictive value (NPV) of EBUS-TBNA in mediastinal staging of

lung cancer are 89% (46%-97%) and 91% (60%-99%), respectively.^[1] However, the utility of EBUS-TBNA in lymphoproliferative disorders (LPDs) is still limited.

Lymphoma is a group of blood cell tumors that develop from lymphocytes. It accounts for about 10% of primary mediastinal tumors. Hodgkin disease (HD) represents up to 70% of mediastinal lymphomas, while non-Hodgkin lymphoma (NHL) comprises approximately 25%.^[2] The World Health Organization recommends the diagnosis and subclassification of lymphoma based on the identification of morphologic, phenotypic, genotypic, and molecular features.^[3] Therefore, it is regarded that excisional biopsies through invasive procedures such as mediastinoscopy, thoracoscopy, or thoracotomy are needed in lymphoma. However, these mediastinal

Access this article online	
Quick Response Code: 	Website: www.eusjournal.com
	DOI: 10.4103/2303-9027.175884

Address for correspondence

Dr. Fayez Kheir, Department of Pulmonary Diseases, Critical Care and Environmental Medicine, Tulane University Health Sciences Center, New Orleans, Louisiana, USA. E-mail: fkheir@tulane.edu

Received: 2014-11-25; Accepted: 2015-03-09

core needle biopsies are associated with higher costs, morbidity, and mortality.^[4]

In this study, we performed a systematic review on published trials to evaluate the role of EBUS-TBNA sampling of the mediastinal lymph nodes in patients with suspected lymphoma.

MATERIALS AND METHODS

Search strategy

The search strategy was developed by FK and AI. A librarian with experience in developing search strategies was consulted for developing the strategy further. The following biomedical databases were searched: PubMed, EMBASE, MEDLINE, Cochrane Library Plus, and ISI Web of Knowledge for relevant studies published up to September 2014. Phrases and terms that were used commonly in all databases were “endobronchial ultrasound” OR “endobronchial ultrasonography” OR “EBUS” OR “endobronchial ultrasound-guided” AND “transbronchial needle aspiration” OR “TBNA” AND “lymphoma” OR “lymphoproliferative disorders” OR “lymphadenopathy”. References to articles identified were also searched manually. Only English-language papers were selected.

Study selection

Only full-text articles that described the role of EBUS-TBNA in lymphoma or suspected lymphoma were selected. Both prospective and retrospective studies were included in our study. Case studies, letter reports, conference abstracts, and studies reporting fewer than eight lymphoma patients or pediatric patients were excluded from this review. The results of EBUS-transbronchial needle forceps biopsy or EBUS applications other than convex probe EBUS (CP-EBUS) were not considered. All data were verified for internal consistency, and discrepancy was resolved by discussion among all reviewers.

Three reviewers (FK, AI, and OA) independently judged the study eligibility while screening the citations. Disagreements were resolved by discussion and consultation with a fourth author (AA). The fourth author was involved in the writing, editing, and conduct of the discussion. In order to ensure consistency, we conducted calibration exercises and pilot test to screen forms prior to starting the process.

Data abstraction and quality assessment

The following information was obtained from each study: Publication type (title, first author, center in which

the study was done, time frame of each trial, and date published), study design, patients’ history of lymphoma, other interventions if any to provide a definitive diagnosis, lymph node size, and clinical follow-up. All data were verified for internal consistency, and discrepancy was resolved by discussion among all reviewers.

The quality of evidence presented in the studies was evaluated independently by two authors (FK and AI) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.^[5] Disagreements were resolved by discussion with the fourth author (AA).

RESULTS

Overview of eligible trials

The bibliographic search yielded 203 papers. Titles and abstracts were reviewed and 197 publications were excluded based on our exclusion criteria. The remaining six full-text articles involving 346 patients were subsequently selected for further analysis.^[6-11]

Characteristics and quality of selected studies

The main characteristics of eligible studies are described in Table 1. All were conducted in single centers. Three studies were performed in the USA,^[6,7,9] one in Turkey,^[10] one in the UK,^[11] and one in Australia.^[8] A dedicated 22-gauge needle was used for aspiration from targeted mediastinal/hilar lymphadenopathy under real-time ultrasound guidance in all studies^[6-8,10,11] except in the case of Iqbal *et al.*,^[9] where a 21-gauge needle was used. An average of three passes per lymph node station was done in all studies,^[6-10,12] except in the case of Moonim *et al.*^[11] where a mean of 5.1 passes were done. None of the authors mentioned whether suction was applied to EBUS-guided biopsies sampling or not. The regional lymph node stations of the mediastinum and hilar were systematically imaged and measured (diameter of short axis) using the 1997 International Staging System was used until the updated International Association for the Study of Lung Cancer lymph node map was published in 2009, which was used thereafter.^[12,13] According to the GRADE scale,^[5] the level of evidence was moderate in one study^[11] and low in all the remaining studies.^[6-10]

Effectiveness of EBUS-TBNA in lymphoma

Moonim *et al.*^[11] conducted the largest prospective trial ($n = 100$) that evaluated the role of EBUS-TBNA in subtype diagnosis of *de novo* and relapsed mediastinal lymphomas in

Table 1. Results of studies that assess the effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration in lymphoma

Author	Type of study	Patients/procedures included	Reference/comparison test	Diagnostic performance					Complications
				S	Sp	PPV	NPV	Diagnostic Accuracy	
Marshall ^[7]	Retrospective	33 patients with history of lymphoma or new isolated mediastinal lymphadenopathy identified on computed tomography	Positive cytology and histology as final diagnoses Mediastinoscopy (n=3) Clinical and radiological follow-up	—	—	—	—	—	None
Moonim ^[11]	Prospective	100 patients with denovo or suspected relapsed mediastinal lymphoma	Positive cytology and histology as final diagnoses Mediastinoscopy (n=20) Bone marrow biopsy (n=4) Excision lung biopsy, liver, buttock and paraspinal masses (n=4)	89%	97%	98%	83%	91%	None
Senturk ^[10]	Retrospective	68 patients with suspected lymphoma on the basis of history of lymphoma or newly isolated mediastinal identified on computed tomography	Positive cytology and histology as final diagnoses Mediastinoscopy (n=3) Thoracotomy (n=1)	86.7%	100%	100%	96.4%	97%	None
Steinfort ^[8]	Retrospective	55 patients with isolated mediastinal or hilar lymphadenopathy and suspected lymphoma	Positive cytology and histology as final diagnoses. Mediastinoscopy (n=9)	57%	100%	100%	87%	—	None
Iqbal ^[9]	Retrospective	65 patients with mediastinal or hilar involvement or both or a combination of other biopsy specimens and positive radiographic criteria	Positive cytology and histology as final diagnoses Mediastinoscopy (n=17) Biopsy at other sites (n=23)	38%	—	—	—	—	None
Kennedy ^[6]	Retrospective	25 patients with suspected lymphoma (clinical, radiological data or other previous lymphoma)	Positive cytology and histology as final diagnoses Mediastinoscopy (n=1) Clinical and radiological follow-up	91%	100%	100%	93%	96%	None

S: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value

2013. The overall sensitivity, specificity, positive predictive value (PPV), NPV, and accuracy were 89%, 97%, 98%, 83%, and 91%, respectively. *De novo* lymphoma was correctly diagnosed in 88% patients and relapsed lymphoma in 100% patients. The mean lymph node size was 1.61 cm (0.5-4 cm). EBUS-TBNA diagnosis was adequate for clinical management in 84% of cases. The sensitivity of subtyping of high-grade NHL, low-grade NHL, and HD were 90%, 100%, and 79%, respectively.

In a retrospective study done by Senturk and colleagues^[10] in 2014, the sensitivity, specificity, NPV, and diagnostic accuracy of EBUS-TBNA in lymphoma were 86.7%, 100%, 96.4%, and 97%, respectively, for the diagnosis of lymphoma. The diagnostic

sensitivity of EBUS-TBNA in establishing a definitive diagnosis in isolated mediastinal (benign or malignant) lymphadenopathy was 94%, and adequate sampling was obtained in 97% of the patients. The median lymph node size was 1.5 cm (0.5-5 cm). Of the 15 lymphoma patients, 10 were diagnosed with HD, three with follicular lymphoma, and two with large B-cell lymphoma. There were only two patients with relapsed lymphoma diagnosed correctly with EBUS-TBNA. There were two false-negative diagnoses reported in this study.

Iqbal *et al.*^[9] reported that the overall sensitivity of EBUS-TBNA in establishing a definitive diagnosis of lymphoma is 38%. However, specificity, PPV, and NPV were not reported. Primary lymphoma was correctly

diagnosed in 22% and recurrent lymphoma in 55% of the patients.

Another trial published by Marshall *et al.*^[7] in 2011 included 33 patients with suspected lymphoma who underwent EBUS-TBNA. Eight patients were diagnosed with lymphoma (six recurrent). Nineteen patients had benign disease confirmed by EBUS-TBNA. Two cases were suspicious for HD and confirmed by core biopsy. Two patients were diagnosed as having atypical cells (one patient underwent mediastinoscopy that showed granulomatous inflammation, and the other had repeat EBUS-TBNA that showed HD). In three patients, the lymph node samples were insufficient for diagnosis, but none developed lymphoma. Adequate diagnostic specimen was obtained in 85% of the cases. There were no false-positive or false-negative diagnoses reported in this study.

Kennedy and colleagues^[6] also described the use of EBUS-TBNA in lymphoma and reported sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 91%, 100%, 100%, 93%, and 96%, respectively. Adequate samples were obtained in 96% of the patients. The mean lymph node size was 1.2 cm (0.7-2.7 cm). In patients with prior history of lymphoma, EBUS-TBNA was able to correctly diagnose all recurrences. In patients presenting with mediastinal lymphadenopathy, there was only one false-negative diagnosis.

Another retrospective study^[8] by Steinfert *et al.* published in 2010 reported sensitivity, specificity, and NPV of 57%, 100%, and 87%, respectively. EBUS-TBNA yielded adequate tissue in 87% of the patients (48/55) and definitive diagnosis in 76% of the patients. Fifty-five patients with suspected lymphoma were included in the study. Twenty-one had a final diagnosis of lymphoma. EBUS-TBNA revealed lymphoma in 16 patients; however, four patients required surgical biopsy for subclassification to guide therapy. Five of 21 lymphoma patients were nondiagnostic by EBUS-TBNA. Surgical procedures were required to diagnose HD, marginal zone lymphoma, and fully classify demonstrated B-cell NHL.

Safety

None of the studies reported complications related to EBUS-TBNA.

DISCUSSION

The results of the studies presented in this systematic review indicate that real-time EBUS-TBNA is safe

and can be considered as the first modality in patients with suspected lymphoma. However, it is important to recognize that the evidence for the use of EBUS-TBNA in such a population is derived mostly from retrospective, nonrandomized, and noncontrolled studies with relatively low numbers of patients. The overall sensitivity, NPV, and diagnostic accuracy ranged 38%-91%, 83%-96.4%, and 91%-97%, respectively.^[6-11] Adequate sampling exceeded 80% in all studies. The sensitivity, NPV, and diagnostic accuracy in recurrent lymphoma ranged 67%-100%, 83%-100%, and 88%-100%, respectively.^[6,8,10,11] The sensitivity, NPV, and diagnostic accuracy in *de novo* lymphoma ranged 64%-88%, 76%-91%, and 83%-92%, respectively.^[6,8,10,11] Further invasive surgical interventions such as mediastinoscopy or thoracotomy to confirm diagnosis were needed only in 13%-43% of all patients diagnosed with lymphoma.

The lowest sensitivity of EBUS-TBNA in patients with suspected lymphoma was reported by Iqbal *et al.*^[9] Several reasons could have contributed to such low sensitivity. Flow cytometry was not used routinely when evaluating EBUS-TBNA specimens. Also, the study did not mention whether rapid on-site cytologic evaluation (ROSE) was done during each procedure. In fact, Ko and colleagues^[14] stress the importance of ROSE by cytopathologists to ensure adequacy and minimize specimen utilization for nonspecific assays. They showed that EBUS-TBNA provides sufficient samples for definitive primary diagnosis and classification of malignant lymphoma through providing adequate material for ancillary studies such as immunohistochemical staining, flow cytometry, fluorescence *in situ* hybridization (FISH), and microbiologic studies. Furthermore, specific subtypes of lymphoma such as hypocellular HD, marginal zone, and follicular lymphomas might be difficult to definitely diagnose in low-volume specimens.^[15] Moomin *et al.*^[11] reported the only study that showed lower sensitivity of HD as compared to other subtypes. Furthermore, some investigators have reported that the diagnostic yield of EBUS-TBNA increased with respect to HD and NHL when biopsy forceps was introduced through the hole made by the TBNA needle to obtain histologic material either blindly or under fluoroscopic or EBUS guidance.^[16-19]

The other published analysis that reported low sensitivity was done by Steinfert and colleagues.^[8] On closer examination, they had only two patients with history of lymphoma as compared to the other studies,^[6,7,9-11]

where there were higher numbers of patients with history of lymphoma. The presence of malignant cells without exact subclassification in patients with relapsed lymphoma is often sufficient to establish recurrence and guide therapy. In addition, repeating mediastinoscopy is difficult in patients with relapsed lymphomas due to adhesions and fibrotic changes in the mediastinum caused by chemotherapy and radiation therapy. Thus, EBUS-TBNA might be preferred in such a population, although technical difficulties might be expected with EBUS in patients with a history of mediastinoscopy or chemotherapy and radiation therapy.^[20]

There are several limitations to generalizing these results. First, the diagnostic performance of EBUS-TBNA in lymphoma was not compared directly to a gold-standard surgical procedure such as mediastinoscopy. The only prospective trial that directly compared these two modalities was in patients with suspected lung cancer.^[21] EBUS-TBNA demonstrated significantly higher sensitivity (91% *vs.* 78%; $P = 0.007$), primarily due to the ability of EBUS-TBNA to sample posterior subcarinal lymph nodes.^[21] Although it is widely accepted that positive results of EBUS-TBNA in other cancers such as lung cancer do not need to be confirmed by further surgical intervention, the accurate assessment of diagnostic yield of EBUS-TBNA in lymphoma is still debatable. Second, studies are very heterogeneous with respect to patient selection (suspicion of lymphoma or history of lymphoma), diagnostic yield, and lymphoma tumor subtypes. The study by Moonim *et al.* was the only study that reported sensitivity in different subtypes.^[11] Third, there is an evident lack of multicenter trials that evaluate diagnostic performance of EBUS-TBNA in lymphoma, as all the studies were done in a single center.

CONCLUSION

EBUS-TBNA is a minimally invasive procedure that can be regarded as an initial evaluation in patients with mediastinal lymphadenopathy and suspected lymphoma. It has a higher yield in recurrent lymphoma than in the diagnosis of newly suspected lymphoma.

An important limitation of the present study is the absence of a meta-analysis and the low-quality evidence. However, we got the impression that at present it is practically impossible to perform meta-analysis due to the great variability regarding lymphoma histology, procedure protocol, and interpretation of results.

The presence of cytopathologists for ROSE and facilitation of ancillary studies as well transbronchial needle forceps might yield an accurate diagnosis and subclassification of lymphomas. Surgical biopsy may be necessary if the sample is inadequate for diagnosis or the subclassification of the lymphoma.

REFERENCES

1. Silvestri GA, Gonzalez AV, Jantz MA, *et al.* Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2013;143 (Suppl):e211S-50S.
2. Duwe BV, Sterman DH, Musani AI. Tumors of the mediastinum. *Chest* 2005;128:2893-909.
3. Swerdlow SH, Campo E, Harris NL, *et al.* WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008.
4. Kiser AC, Detterbeck FC. General aspects of surgical treatment. In: Detterbeck FC, Rivera MP, Socinski MA, *et al.*, editors. Diagnosis and Treatment of Lung Cancer: An Evidence-Based Guide for the Practicing Clinician. Philadelphia, PA: WB Saunders; 2001. p. 133-47.
5. Balshem H, Helfand M, Schünemann HJ, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64:401-6.
6. Kennedy MP, Jimenez CA, Bruzzi JF, *et al.* Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. *Thorax* 2008;63:360-5.
7. Marshall CB, Jacob B, Patel S, *et al.* The utility of endobronchial ultrasound-guided transbronchial needle aspiration biopsy in the diagnosis of mediastinal lymphoproliferative disorders. *Cancer Cytopathol* 2011;119:118-26.
8. Steinfurt DP, Conron M, Tsui A, *et al.* Endobronchial ultrasound-guided transbronchial needle aspiration for the evaluation of suspected lymphoma. *J Thorac Oncol* 2010;5:804-9.
9. Iqbal S, DePew ZS, Kurtin PJ, *et al.* Endobronchial ultrasound and lymphoproliferative disorders: A retrospective study. *Ann Thorac Surg* 2012;94:1830-4.
10. Senturk A, Babaoglu E, Kilic H, *et al.* Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. *Asian Pac J Cancer Prev* 2014;15:4169-73.
11. Moonim MT, Breen R, Fields PA, *et al.* Diagnosis and subtyping of *de novo* and relapsed mediastinal lymphomas by endobronchial ultrasound needle aspiration. *Am J Respir Crit Care Med* 2013;188:1216-23.
12. Mountain C, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997;111:1718-23.
13. Rusch VW, Asamura H, Watanabe H, *et al.*; Members of IASLC Staging Committee. The IASLC lung cancer staging project: A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:568-77.
14. Ko HM, da Cunha Santos G, Darling G, *et al.* Diagnosis and subclassification of lymphomas and non-neoplastic lesions involving mediastinal lymph nodes using endobronchial ultrasound-guided transbronchial needle aspiration. *Diagn Cytopathol* 2013;41:1023-30.
15. Farmer PL, Bailey DJ, Burns BF, *et al.* The reliability of lymphoma diagnosis in small tissue samples is heavily influenced by lymphoma subtype. *Am J Clin Pathol* 2007;128:474-80.
16. Herth FJ, Morgan RK, Eberhardt R, *et al.* Endobronchial ultrasound-guided miniforceps biopsy in the biopsy of subcarinal masses in patients with low likelihood of non-small cell lung cancer. *Ann Thorac Surg* 2008;85:1874-8.

17. Chrissian A, Misselhorn D, Chen A. Endobronchial-ultrasound guided miniforceps biopsy of mediastinal and hilar lesions. *Ann Thorac Surg* 2011;92:284-8.
18. Oki M, Saka H, Sako C. Bronchoscopic miniforceps biopsy for mediastinal nodes. *J Bronchology Intero Pulmonol* 2004;11:150-3.
19. Prakash UB. A better bronchoscopic technique to obtain diagnostic tissue from mediastinal lymph nodes. *J Bronchology Intero Pulmonol* 2005;12:1-2.
20. Call S, Rami-Porta R, Obiols C, *et al.* Repeat mediastinoscopy in all its indications: Experience with 96 patients and 101 procedures. *Eur J Cardiothorac Surg* 2011;39:1022-7.
21. Ernst A, Anantham D, Eberhardt R, *et al.* Diagnosis of mediastinal adenopathy-real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. *J Thorac Oncol* 2008;3:577-82.

How to cite this article: Kheir F, Itani A, Assasa O, Alraiyes AH. The utility of endobronchial ultrasound-transbronchial needle aspiration in lymphoma. *Endosc Ultrasound* 2016;5:43-8.

Source of Support: There was no financial, pharmaceutical, or funding support. **Conflicts of Interest:** The authors declare that there was no conflict of interest.