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Endobronchial ultrasound-guided transbronchial needle aspiration: a retrospective analysis of 228 patients

Endobronşiyal ultrason rehberliğinde transbronşiyal iğne aspirasyonu:
228 hastanın retrospektif analizi

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ABSTRACT

Background: This study aims to investigate the diagnostic value of endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) procedure in malign and benign diseases.

Methods: Two hundred twenty-eight patients (165 males, 63 females; mean age 58.1 years; range 22 to 84 years) who were performed EBUS-TBNA between April 2011 and January 2013 were retrospectively analyzed. Midazolam sedation was applied in all patients. The diagnostic verification of the samples collected from lymph nodes was carried out by surgical intervention or clinical and radiological follow-up.

Results: In a total of 228 EBUS-TBNA procedures, 1,447 aspirations (average 6.47 for each patient, range 1-12) were applied to 635 lymph nodes (average 2.78 for each patient, range 1-6). In 98.6% of the patients (225/228), the samples were histopathologically appropriate. The histopathological examination identified 88 reactive hyperplasias (39%), 82 neoplastic diseases (36%), 39 granulomatous diseases (17%) (tuberculosis compatible in four patients), and five patients with suspicion of malignant diseases (2%). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rates were 91.7%, 100%, 100%, 88.9%, and 95%, respectively. No mortality was observed associated with EBUS-TBNA procedure.

Conclusion: This study suggests that EBUS-TBNA is a reliable method with high diagnostic value in the evaluation of the mediastinal and hilar lymph nodes.

Keywords: Endobronchial ultrasound, mediastinal and hilar lymph node, transbronchial needle aspiration.

ÖZ

Amaç: Bu çalışmada, malign ve benign hastalıklarda endobronşiyal ultrason rehberliğinde transbronşiyal iğne aspirasyonu (EBUS-TBİA) işleminin tanısal değeri araştırıldı.

Çalışma planı: Nisan 2011 - Ocak 2013 tarihleri arasında EBUS-TBİA uygulanan 228 hasta (165 erkek, 63 kadın; ort. yaş 58.1 yıl; dağılım 22-84 yıl) retrospektif olarak incelendi. Tüm hastalara midazolam sedasyonu uygulandı. Lenf nodlarından alınan örneklerin tanısal doğrulaması cerrahi girişim veya klinik ve radyolojik takip ile yapıldı.

Bulgular: Toplam 228 EBUS-TBİA işleminde 635 lenf noduna (her hasta için ortalama 2.78, dağılım 1-6) 1447 aspirasyon (her hasta için ortalama 6.47, dağılım 1-12) uygulandı. Hastaların %98.6'sında (225/228) örnekler histopatolojik olarak uygun idi. Histopatolojik incelemede 88 reaktif hiperplazi (%39), 82 neoplastik hastalık (%36), 39 granülomatöz hastalık (%17) (dört hasta tüberküloz ile uyumlu) ve malign hastalıktan şüphelenilen beş hasta (%2) saptandı. Hassasiyet, özgüllük, pozitif öngörü değeri, negatif öngörü değeri ve doğruluk oranları sırasıyla %91.7, %100, %100, %88.9 ve %95 idi. EBUS-TBİA işlemine bağlı mortalite gözlenmedi.

Sonuç: Bu çalışma mediastinal ve hiler lenf nodlarının değerlendirilmesinde EBUS-TBİA'nın güvenli ve tanısal değeri yüksek bir yöntem olduğuna işaret etmektedir.

Anahtar sözcükler: Endobronşiyal ultrason, mediastinal ve hiler lenf nodu, transbronşiyal iğne aspirasyonu.

Noninvasive diagnostic tools, such as computed tomography (CT) and positron emission tomography (PET), are frequently used as standard imaging methods in the evaluation of mediastinal lymph nodes. However, using these two methods to differentiate between those that are malignant and those that are benign is still not possible in clinical evaluations.[1,2] In these situations, evaluating the pathological lymph nodes with accuracy is possible through the use of a mediastinoscopy, the current gold standard. However, this method is invasive, requires hospitalization and general anesthesia, and has low complication risks, although at relatively low rates.[3-5] In recent years, transbronchial needle aspiration (TBNA) with real time endobronchial ultrasound (EBUS) has been routinely used to histopathologically evaluate the mediastinal and hilar lymph nodes. It is a minimally invasive technique with high diagnostic accuracy and can also be used to collect samples for cytological evaluation. In addition, meta-analyses have shown that the sensitivity of the EBUS-TBNA method is above 88%.[6-8] The aim of this study was to evaluate the diagnostic performance and process reliability of the EBUS-TBNA method in the cytological evaluation of patients with mediastinal and hilar lymph nodes and examine the clinical features of these cases.

PATIENTS AND METHODS

The clinical and pathological features of 228 patients (165 males, 63 females; mean age 58.1 years; range 22-84 years) who received EBUS-TBNA between April 2011 and January 2013 were retrospectively analyzed. All the patients gave their informed consent to be included in the study before the procedure was performed.

The patients underwent EBUS-TBNA because of suspected mediastinal lymph node metastasis based on the CT (short axis of lymph node >1 cm) or PET/CT (FDG uptake ≥2.5) results.[9] The EBUS-TBNA team consisted of an implementing physician, an anesthesia technician, a nurse, and an auxiliary staff member. Intravenous midazolam (0.05 mg/kg) was used for conscious sedation after a minimum of four hours of fasting, and we introduced the BF-UC180F linear ultrasound bronchoscope (Olympus Medical Systems Corp., Tokyo, Japan) and used either the single-use 22-gauge (22G) EBUS-TBNA aspiration needle (Olympus Medical Systems Corp., Tokyo, Japan) or the Echo Tip® Ultra Endobronchial High Definition Ultrasound Needle (Cook Medical. Bloomington, IN, USA) during the procedure.

In the cancer patients, if there were multiple lymph node involvement, we started with the lymph node stations that presented with the worst prognosis (N3 prior to N2) to prevent cross-contamination. In addition, if multiple lymph node stations were biopsied, a single TBNA needle was used for each station after flushing the working channel with normal saline. The goal was to perform an accurate staging with a single needle.

The minimum diameter of the lymph nodes that were localized by EBUS-TBNA and biopsied was 5 mm. For each patient, a minimum of two lymph node stations were evaluated, and for each one, a maximum of five aspirations were conducted. The "Doppler ultrasound mode" was used as necessary to differentiate this tissue from the biopsy tissue taken from the vascular structure.

The aspiration materials on which this procedure was performed were both fixed by 95% ethyl alcohol, and the cell blocks were prepared using the CytoRich Red® preservative fluid (Tripath Imaging, Inc., Burlington, NC). During the EBUS-TBNA procedure, no on-site cytopathologist was available in the bronchoscopy department of the hospital, so the appropriateness of the cytological materials was defined by the presence of lymphocytes, pigmented macrophages, histiocyte clusters, and neoplastic cells. The aspirates with an insufficient number of lymphoid cells, crush artifacts, or erythrocytes along with those only bronchial cells were considered to be inappropriate for a diagnosis. In the biopsy material, the presence of lymphoid tissue (lymphocytes, histiocytes, anthracosis residue, or macrophages) or neoplastic cells was interpreted as being suitable for diagnosis. The unsuitable aspiration materials were reviewed again by another cytopathologist, but the diagnosis did not change.

The sensitivity, specificity, and positive and negative predictive values of the EBUS-TBNA were analyzed according to the aspiration results and had been confirmed either by the surgical intervention or clinical and radiological treatment.

RESULTS

The lymph node aspiration was conducted in the following lymph node stations: subcarinal (n=261), lower paratracheal (n=215), hilar (n=152), and upper paratracheal (n=7). A total of 635 evaluated lymph nodes (mean of 2.78 lymph nodes per patient; range 1-6), and 1,447 lymph node aspirations (mean of 6.47 per patient; range 1-12) were performed. However, EBUS-TBNA was not carried out on any patient who

Table 1. Patient characteristics

	n	%	Median	Range
Number of patients	228			
Gender				
Females	63			
Males	165			
Median age in years			58.1	22-84
Primary diagnosis				
Bronchial carcinoma	106	46.5		
Pure mediastinal lymphadenomegalia	65	28.5		
Lung mass	22	10		
Breast carcinoma	10	4		
Non-small cell lung cancer (with neoadjuvant therapy)	7	3		
Non-small cell lung cancer (operated)	4	1.5		
Paratracheal mass	5	2		
Colon adenocarcinoma	3	1.5		
Ewing's sarcoma	1	0.5		
Endometrial carcinoma	1	0.5		
Bladder carcinoma	1	0.5		
Malignant melanoma	1	0.5		
Rectal carcinoma	1	0.5		
Teratoma	1	0.5		

had possible hilar lymph node metastases without any possible metastatic mediastinal lymph nodes. Additionally, no hilar lymph node metastases were detected by EBUS-TBNA without the presence of any mediastinal lymph node metastases.

In the majority of the patients who underwent EBUS-TBNA, the primary diagnoses were bronchial carcinoma (n=106, 46.5%), pure mediastinal lymphadenopathy (n=65, 28.5%), and an undiagnosed pulmonary mass with clinically abnormal mediastinal lymph nodes (n=22, 10%). These pulmonary masses were not diagnosed by conventional fiberoptic bronchoscopy or transthoracic fine needle aspiration because they were not available at our facility. There were 19 patients (8.5%) with metastatic non-pulmonary carcinoma, and 10 with breast carcinomas (4%) along with three with colonic carcinomas (1.5%), and these were the most common primary tumors that metastasized to the mediastinal lymph nodes. The characteristics of the patients are shown in Table 1.

All of the patients in the study who had been primarily diagnosed with non-small cell lung cancer (NSCLC) were surgical resection candidates if they had no locally advanced diseases. When the post-EBUS cytopathological results were analyzed, 88 (39%) were diagnosed with reactive lymph nodes, 82 (36%) with metastatic lymph nodes, and 39 (17%) with granulomatous disease. In addition, false negative

results were confirmed during the surgery in 11 of the remaining 18 patients.

When the cytopathological results of the 22 patients that underwent EBUS-TBNA for an undiagnosed pulmonary mass with clinically abnormal mediastinal lymph nodes were evaluated, the results revealed bronchial carcinoma in 13 patients (eight with squamous cell carcinoma and five with small cell carcinoma), metastatic lymph nodes (NSCLC with no subgroup assignment) in one patient, reactive hyperplasia in six others, granulomatous disease in one, and suspicious material in another.

The cytopathological results of the five patients who underwent the EBUS-TBNA procedure due to a paratracheal mass were analyzed, and NSCLC (2 squamous cell carcinoma and 1 spindle cell carcinoma) was identified in three patients, small cell carcinoma in one, and granulomatous disease compatible with tuberculosis (TB) in another.

The 121 patients (53%) identified with a specific disease (metastatic or granulomatous disease) were not confirmed surgically. However, confirmation for 65 patients (28%) with reactive lymph nodes occurred via a surgical procedure and for 43 (19%), it took place via clinical or radiological monitoring for at least six months. In all of the patients being monitored, the lymph nodes had either remained stable or receded (Table 2). In the 54 patients (54.5%) diagnosed with

Table 2. Cytopathological results of the mediastinal and hilar lymph nodes in study patients

Cytopathological results	n	%
Reactive hyperplasia	88	39
Neoplastic disease	82	36
Squamous cell carcinoma	52	23
Adenocarcinoma	18	8
Small cell carcinoma	8	3
Malignant disease (unclassified)	2	1
Spindle cell tumor	1	0.5
Neuroendocrine tumor	1	0.5
Granulomatous disease	39	17
Sarcoidosis	35	15
Tuberculosis	4	2
False negative	11	5
Suspicious material	5	2
Inappropriate material	3	1
Total	228	100

reactive hyperplasia by EBUS who received surgical intervention, the diagnosis did not change; however, in the remaining 11 patients (11.1%), the reactive hyperplasia that had been diagnosed by this technique was identified as granulomatosis in five cases and malignant disease in six others via invasive surgical interventions. The overall false negativity rate was 5% (11/228). Three of these false negative patients had less than two aspirations, and the short axis of the lymph nodes was smaller than 1 cm in two others. The highest rate of false negative results by EBUS was obtained from the right paratracheal lymph nodes (station 4R) (Table 3). Furthermore, seven upper paratracheal lymph nodes (station 2R) were diagnosed as reactive hyperplasia, and this was confirmed during the surgical intervention.

Afterwards, a histopathological analysis found granulomatous disease. Moreover, the angiotensin receptor blocker (ARB) culture results of the material conducted by EBUS-TBNA were positive.

In the patients with benign diseases, the sensitivity, specificity, positive predictive values, negative predictive values, and diagnostic accuracy for the EBUS-TBNA procedure were 88.6%, 100%, 100%, 94.6%, and 96.2%, respectively, but for those with malignant diseases, the rates were 93.2%, 100%, 100%, 93.6%, and 96.6%. In addition, the overall rates for these values were 91.7%, 100%, 100%, 88.9%, and 95.0%, respectively.

In five patients, TBNA was performed once per lymph node due to problems that occurred during the procedure. Three had hemoptysis, one suffered a hypertensive attack, and another had cardiac arrhythmia. For the patients with hemoptysis, the mild endobronchial bleeding was controlled with a cold saline and adrenaline solution before the procedure was completed, whereas the hypertensive attack and cardiac arrhythmia were treated with medication. No mortality was associate with the EBUS-TNBA procedure.

DISCUSSION

Conventional TBNA, a blinded technique performed using a fiberoptic bronchoscope, has been used for more than 30 years.[10] Although this method can be used to take samples from the hilar and mediastinal lymph nodes, it is more effective in the subcarinal and right paratracheal stations.[11-14] Moreover, identifying the small lymph nodes (target visualization) and performing biopsies on these lymph nodes with the conventional EBUS-TBNA procedure

Table 3. Characteristics of the false negative cases

Primary diagnosis of patients	Cytopathological results of EBUS-TBNA	Histopathological results of invasive procedures	False negative lymph node station
Non-small cell lung cancer	Reactive hyperplasia	Malignant	Subcarinal (7)
Bladder carcinoma	Reactive hyperplasia	Granuloma	Right paratracheal (4R)
Mediastinal lymphadenomegalia	Reactive hyperplasia	Granuloma	Right paratracheal (4R)
Non-small cell lung cancer	Reactive hyperplasia	Malignant	Subcarinal (7)
Ewing's sarcoma	Reactive hyperplasia	Malignant	Right paratracheal (4R)
Non-small cell lung cancer	Reactive hyperplasia	Granuloma	Right paratracheal (4R)
Non-small cell lung cancer	Reactive hyperplasia	Granuloma	Right paratracheal (4R)
Mediastinal lymphadenomegalia	Reactive hyperplasia	Granuloma (TB)	Right paratracheal (4R)
Non-small cell lung cancer	Reactive hyperplasia	Malignant	Left paratracheal (4L)
Paratracheal mass	Reactive hyperplasia	Malignant	Right paratracheal (4R)
Breast carcinoma	Reactive hyperplasia	Malignant	Right paratracheal (4R)

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration.

Table 4. Diagnostic performance of the study population

	Benign diseases	Malignant diseases	All diseases
	%	%	%
Sensitivity	88.6	93.2	91.7
Specificity	100	100	100
Positive predictive value	100	100	100
Negative predictive value	94.6	93.6	88.9
Diagnostic accuracy	96.2	96.6	95.0

is difficult. Additionally, Cetinkaya et al.[15] found that in conventional EBUS-TBNA, the sensitivity and diagnostic rates were high in cases with negative histopathological results.

A mediastinoscopy is a surgical method which requires general anesthesia and hospitalization, and it has minimal mortality and morbidity risks. Some studies that have been conducted in recent years have shown that the EBUS-TBNA procedure and mediastinoscopies, which are regarded as the gold standard for the histopathological diagnosis of mediastinal lymph nodes, have the same diagnostic accuracy rates, especially in the second, fourth, and seventh stations.[16,17]

In their study, Yasufuku et al.,[18] stated that 41 (39%) out of the 105 patients who received EBUS-TBNA due to hilar and/or mediastinal adenopathies avoided surgery. Mediastinoscopies were performed on 29 of the patients, thoracotomies on eight, and thoracoscopies on four others.

In our study, 121 (53%) out of the 228 patients had a specific granulomatous or malignant disease which was diagnosed via EBUS-TBNA making the need for surgical intervention to confirm the diagnosis unnecessary. However, this type of confirmation was necessary for 28% (n=65) of the remaining patients because of the presence of reactive hyperplasia, suspicion of a disease, or the use of inappropriate materials. In addition, 19% (n=43) were monitored.

After the first presentation of the EBUS-TBNA procedure in the literature, studies stating that it was accurate and reliable for the cytopathological evaluation of both mediastinal and hilar lymph nodes were published.[19,20] Additionally, some studies have also proposed that the learning period for this technique is relatively short.[21-23]

In the meta-analysis by Varela-Lema et al.[24] that analyzed 14 scientific articles that focused on patients

diagnosed with lung cancer, they determined that the sensitivity ranged from 85-100% and the negative predictive values varied from 11-97.4%. Three studies assessed the clinical applicability of the EBUS-TBNA technique in the diagnosis of sarcoidosis and found that it was used diagnostically in 88-93% of the patients. In another meta-analysis, Gu et al.,[7] evaluated a total of 1,299 cases with lung cancer and determined that the sensitivity of the EBUS-TBNA procedure was 93%. Furthermore, a review of this approach performed on patients suspected of having sarcoidosis found that it had a sensitivity of between 85 and 93%.[25] In our study, the diagnostic value of EBUS-TBNA was relatively low, but this was most likely due to the pathologist's lack of experience. Cetinkaya et al.[26] attributed their high diagnosis rates for benign diseases to the importance of convex probe (CP)-EBUS guidance. In this study, the overall diagnostic accuracy of EBUS-TBNA was consistent with the findings of these studies.

In the patients with both benign and malignant diseases, negative predictive value and diagnostic value as 91.7%, 88.9% and 95% respectively.

Song et al.[27] showed that a definitive diagnosis for the evaluation of nodal metastases from an extrapulmonary malignancy was achieved by EBUS-TBNA in 61.4% (n=35) of 57 patients, allowing them to avoid surgery. Furthermore, Parmaksız et al.[28] evaluated mediastinal and hilar lymph nodes in 48 patients with a history of an extrathoracic malignancy and demonstrated that EBUS-TBNA could be used to accurately diagnose mediastinal lymph node metastases. We had 19 patients (8.3%) with extrathoracic malignancies.

In our study, EBUS-TBNA was performed on 19 patients with an extrapulmonary malignancy, and five of these (26%) had a malignant disease that negated the need for more invasive surgical techniques while surgical intervention revealed that 11 (58%) had benign lymph nodes and three (16%) had false negative results.

The usefulness of rapid on-site evaluation (ROSE) throughout endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for lymph node staging in patients with lung cancer is still debatable. Chandra et al.[8] stated that the sensitivity of EBUS-TBNA was not dependent on ROSE or the size of the needle that was used. Furthermore, Nakajima et al.[29] validated that ROSE done during EBUS-TBNA for material adequacy showed a low rate of nondiagnostic sampling, but there was a high consonance between the on-site and final pathological

evaluations. Nevertheless, careful attention should be paid to the immediate diagnosis. At our institution, we do not perform ROSE; hence, the EBUS-TBNA technique was repeated until an adequate amount of material was collected. Our clinical experience has also shown that in this subjective evaluation, a correlation does not always exist between the amount of material taken and the diagnosis gained by EBUS-TBNA. Furthermore, the researchers in our study used two different brands of transbronchial needles that were the same size, but no difference was seen in terms of applicability.

In the study by Medford et al.,[25] because of the current inferior negative predictive value of EBUS-TBNA, they deemed that a mediastinoscopy was still required for the clarification of negative nodes associated with this technique. However, Zhang et al.[30] found that the diagnostic yield of EBUS-TBNA was still lower than that of transcervical mediastinoscopy and that it appears to not be as dependable for the safe elimination of mediastinal nodal metastases. Therefore, they encouraged the use of a transcervical mediastinoscopy to confirm negative EBUS-TBNA results.

Nowadays, the matter at hand is whether the EBUS-TBNA procedure should replace a mediastinoscopy. With that in mind, it should be noted that a mediastinoscopy is considered to be the gold standard for the histological evaluation of mediastinal lymph nodes, and the European Society of Thoracic Surgeons (ESTS) guidelines recommended that negative EBUS-TBNA results should be verified via surgery or other techniques.[1]

Conclusion

The EBUS-TBNA procedure is a non-invasive technique that can be performed using conscious sedation without the need for general anesthesia, and it requires no hospitalization. In addition, this procedure is reliable and has high diagnostic accuracy rates when pathological mediastinal and/or hilar lymph nodes are evaluated. Therefore, we believe that the opportunity to examine both hilar and interlobar lymph nodes could make this technique a viable choice before invasive interventions are carried out.

Declaration of conflicting interests

Funding

REFERENCES

1. De Leyn P, Lardinois D, Van Schil PE, Rami-Porta R, Passlick B, Zielinski M, et al. ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. Eur J Cardiothorac Surg 2007;32(1):1-8.

2. Cömert SŞ, Çağlayan. A comparision of endobronchial ultrasound-guided transbronchial needle aspiration and integrated positron emission tomography-computed tomography in the diagnosis of malignant mediastinal/hilar lymph nodes. Turk Gogus Kalp Dama 2012;20:843-9.

3. Pillot G, Siegel BA, Govindan R. Prognostic value of fluorodeoxyglucose positron emission tomography in non-small cell lung cancer: a review. J Thorac Oncol 2006;1:152-9.

4. Hammoud ZT, Anderson RC, Meyers BF, Guthrie TJ, Roper CL, Cooper JD, et al. The current role of mediastinoscopy in the evaluation of thoracic disease. J Thorac Cardiovasc Surg 1999;118:894-9.

5. Yasufuku K, Chiyo M, Sekine Y, Chhajed PN, Shibuya K, Iizasa T, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. Chest 2004;126:122-8.

6. Adams K, Shah PL, Edmonds L, Lim E. 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.

7. Gu P, Zhao YZ, Jiang LY, Zhang W, Xin Y, Han BH. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. Eur J Cancer 2009;45:1389-96.

8. Chandra S, Nehra M, Agarwal D, Mohan A. Diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle biopsy in mediastinal lymphadenopathy: a systematic review and meta-analysis. Respir Care 2012;57:384-91.

9. Turkington TG, Coleman RE. Clinical oncologic positron emission tomography: an introduction. Semin Roentgenol 2002;37:102-9.

10. Wang KP, Marsh BR, Summer WR, Terry PB, Erozan YS, Baker RR. Transbronchial needle aspiration for diagnosis of lung cancer. Chest 1981;80:48-50.

11. Wang KP, Brower R, Haponik EF, Siegelman S. Flexible transbronchial needle aspiration for staging of bronchogenic carcinoma. Chest 1983;84:571-6.

12. Harrow EM, Abi-Saleh W, Blum J, Harkin T, Gasparini S, Addrizzo-Harris DJ, et al. The utility of transbronchial needle aspiration in the staging of bronchogenic carcinoma. Am J Respir Crit Care Med 2000;161:601-7.

13. Holty JE, Kuschner WG, Gould MK. Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis. Thorax 2005;60:949-55.

14. Bonifazi M, Zuccatosta L, Trisolini R, Moja L, Gasparini S. Transbronchial needle aspiration: a systematic review on predictors of a successful aspirate. Respiration 2013;86:123-34.

15. Cetinkaya E, Ozgül MA, Tutar N, Ozgül G, Cam E, Bilaçeroglu S. 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.

16. Navani N, Lawrence DR, Kolvekar S, Hayward M, McAsey D, Kocjan G, et al. Endobronchial ultrasound-guided transbronchial needle aspiration prevents mediastinoscopies in the diagnosis of isolated mediastinal lymphadenopathy: a prospective trial. Am J Respir Crit Care Med 2012;186:255-60.

17. Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, 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.

18. Yasufuku K, Nakajima T, Motoori K, Sekine Y, Shibuya K, Hiroshima K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. Chest 2006;130:710-8.

19. Yasufuku K, Chiyo M, Koh E, Moriya Y, Iyoda A, Sekine Y, et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. Lung Cancer 2005;50:347-54.

20. Herth FJ, Eberhardt R, Vilmann P, Krasnik M, Ernst A. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax 2006;61:795-8.

21. Groth SS, Whitson BA, D'Cunha J, Maddaus MA, Alsharif M, Andrade RS. Endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes: a single institution's early learning curve. Ann Thorac Surg 2008;86:1104-9.

22. Bizekis CS, Santo TJ, Parker KL, Zervos MD, Donington JS, Crawford BK, et al. Initial experience with endobronchial ultrasound in an academic thoracic surgery program. Clin Lung Cancer 2010;11:25-9.

23. Kemp SV, El Batrawy SH, Harrison RN, Skwarski K, Munavvar M, Rosell A, et al. Learning curves for endobronchial ultrasound using cusum analysis.Thorax 2010;65:534-8.

24. Varela-Lema L, Fernández-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. Eur Respir J 2009;33:1156-64.

25. Medford AR, Bennett JA, Free CM, Agrawal S. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): applications in chest disease. Respirology 2010;15:71-9.

26. Cetinkaya E, Gunluoglu G, Ozgul A, Gunluoglu MZ, Ozgul G, Seyhan EC, et al. Value of real-time endobronchial ultrasound-guided transbronchial needle aspiration. Ann Thorac Med 2011;6:77-81.

27. Song JU, Park HY, Jeon K, Koh WJ, Suh GY, Chung MP, et al. The role of endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of mediastinal and hilar lymph node metastases in patients with extrapulmonary malignancy. Intern Med 2011;50:2525-32.

28. Parmaksız ET, Caglayan B, Salepci B, Comert SS, Kiral N, Fidan A, et al. The utility of endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal or hilar lymph node evaluation in extrathoracic malignancy: Benign or malignant? Ann Thorac Med 2012;7:210-4.

29. Nakajima T, Yasufuku K, Saegusa F, Fujiwara T, Sakairi Y, Hiroshima K, et al. Rapid on-site cytologic evaluation during endobronchial ultrasound-guided transbronchial needle aspiration for nodal staging in patients with lung cancer. Ann Thorac Surg 2013;95:1695-9.

30. Zhang R, Mietchen C, Krüger M, Wiegmann B, Golpon H, Dettmer S, et al. Endobronchial ultrasound guided fine needle aspiration versus transcervical mediastinoscopy in nodal staging of non small cell lung cancer: a prospective comparison study. J Cardiothorac Surg 2012;7:51.