



doi • 10.5578/tt.66866
Tuberk Toraks 2018;66(2):85-92
Geliş Tarihi/Received: 04.06.2016 • Kabul Ediliş Tarihi/Accepted: 27.04.2018

KLİNİK ÇALIŞMA
RESEARCH ARTICLE

The role of endobronchial and endoscopic ultrasound guided fine needle aspiration for mediastinal nodal staging of non-small-cell lung cancer

Nuri TUTAR¹
Alper YURCİ²
Işın GÜNEŞ³
İnci GÜLMEZ¹
Şebnem GÜRSOY²
Ömer ÖNAL⁴
Özlem CANÖZ⁵

¹ Department of Chest Diseases, Faculty of Medicine, Erciyes University, Kayseri, Turkey

¹ Erciyes Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Kayseri, Türkiye

² Division of Gastroenterology, Faculty of Medicine, Erciyes University, Kayseri, Turkey

² Erciyes Üniversitesi Tıp Fakültesi, Gastroenteroloji Bilim Dalı, Kayseri, Türkiye

³ Department of Anesthesiology and Reanimation, Faculty of Medicine, Erciyes University, Kayseri, Turkey

³ Erciyes Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Kayseri, Türkiye

⁴ Department of Thoracic Surgery, Faculty of Medicine, Erciyes University, Kayseri, Turkey

⁴ Erciyes Üniversitesi Tıp Fakültesi, Göğüs Cerrahisi Anabilim Dalı, Kayseri, Türkiye

⁵ Department of Pathology, Faculty of Medicine, Erciyes University, Kayseri, Turkey

⁵ Erciyes Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, Kayseri, Türkiye

SUMMARY

The role of endobronchial and endoscopic ultrasound guided fine needle aspiration for mediastinal nodal staging of non-small-cell lung cancer

Introduction: Mediastinal and hilar nodal staging is one of the key points for differentiating treatment modalities in patients with non-small-cell lung cancer (NSCLC). The aim of the present study was to determinate the diagnostic yields of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and combined EBUS-TBNA and EUS-FNA modalities for nodal staging in potentially operable NSCLC patients.

Materials and Methods: Twenty consecutive patients were prospectively enrolled in the study between March 2014 and November 2015. All patients had a potentially operable NSCLC diagnosis before endosonographic procedures.

Results: Thirty lymph nodes were sampled by EBUS-TBNA and 17 lymph nodes were sampled by EUS-FNA in all 20 patients. The sensitivity, specificity, positive predictive value, negative predictive

Yazışma Adresi (Address for Correspondence)

Dr. Nuri TUTAR

Erciyes Üniversitesi Tıp Fakültesi, Gevher Nesibe Hastanesi, Göğüs Hastalıkları Anabilim Dalı, KAYSERİ - TÜRKİYE
e-mail: drnuritur@gmail.com

value and diagnostic accuracy of F-18 fluorodeoxyglucose positron emission tomography with computed tomography (PET-CT), EBUS-TBNA, EUS-FNA and combined EBUS-TBNA and EUS-FNA were 100%, 33.3%, 64.7%, 100% and 70.0%; 81.8%, 100%, 100%, 81.8% and 90%; 81.8%, 100%, 100%, 75% and 88.2%; 90.9%, 100%, 100%, 90.0% and 95.0%, respectively.

Conclusion: The combined EBUS-TBNA and EUS-FNA technique is a successful procedure for nodal staging in potentially operable NSCLC patients.

Key words: Cancer staging, non-small-cell lung cancer (NSCLC), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA).

ÖZET

Küçük hücreli dışı akciğer kanserinde endobronşiyal ve endoskopik ultrason rehberliğinde ince iğne aspirasyonunun mediastinal nodal evrelemedeki rolü

Giriş: Küçük hücreli dışı akciğer kanseri (KHDAK) hastalarında değişik tedavi modalitelerini değerlendirmek için anahtar noktalardan birisi mediastinal ve hiler nodal evrelemedir. Bu çalışmanın amacı endobronşiyal ultrason rehberliğinde transbronşiyal iğne aspirasyonu (EBUS-TBNA), endoskopik ultrason rehberliğinde ince iğne aspirasyonu (EUS-İİA) ve kombine EBUS-TBNA ile EUS-İİA'nın potansiyel olarak ameliyat edilebilecek hastalarda nodal evrelemedeki tanı başarısını saptamaktır.

Materyal ve Metod: Mart 2014 ve Kasım 2015 tarihleri arasında ardi ardına 20 hasta çalışmaya dahil edildi. Tüm hastalar endosonografik işlemler öncesi potansiyel olarak ameliyat olabilecek KHDAK tanısı almıştı.

Bulgular: Yirmi hastada EBUS-TBNA ile 30 lenf nodu, EUS-İİA ile 17 lenf nodu örneklendi. F-18 florodeoksiglukoz pozitron emisyon tomografi-bilgisayarlı tomografi (PET-BT), EBUS-TBNA, EUS-İİA ve kombine EBUS-TBNA ile EUS-İİA'nın sensitivite, spesifite, pozitif tahmini değer, negatif tahmini değer ve tanı başarısı sırasıyla %100, %33.3, %64.7, %100 ve %70.0; %81.8, %100, %100, %81.8 ve %90; %81.8, %100, %100, %75 ve %88.2; %90.9, %100, %100, %90.0 ve %95.0'di.

Sonuç: Kombine EBUS-TBNA ile EUS-İİA tekniği potansiyel olarak ameliyat olabilecek KHDAK hastalarının nodal evrelemede başarılı bir yöntemdir.

Anahtar kelimeler: Kanser evrelemesi; küçük hücreli dışı akciğer kanseri (KHDAK); endobronşiyal ultrason rehberliğinde transbronşiyal iğne aspirasyonu (EBUS-TBNA); endoskopik ultrason rehberliğinde ince iğne aspirasyonu (EUS-İİA)

INTRODUCTION

Mediastinal and hilar nodal staging is one of the key points for differentiating treatment modalities in patients with non-small-cell lung cancer (NSCLC). Nodal staging is done radiologically, endosonographically or by surgery. Histological confirmation is suggested although radiological methods indicate mediastinal or hilar nodal metastasis because of false positive results (1-3). Guidelines recommend endosonographic modalities for obtaining histologic material before surgical methods (1,4). This recommendation is based on the sufficient results obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) as minimally invasive methods which are almost similar to those of surgical methods (5-8).

Today, the main problem with EBUS-TBNA and/or EUS-FNA for nodal staging in NSCLC patients is the occurrence of false negative results. Pathologists complain about the small cytological samples obtained by EBUS-TBNA and/or EUS-FNA. At the same time, these procedures can not reach all hilar and mediastinal

lymph nodes separately. Nowadays, the recommendation is to perform EBUS-TBNA and EUS-FNA together in nodal staging of NSCLC patients to decrease false negative results, to obtain further cytological specimens and to reach more lymph nodes (1,4,5). The aim of the present study was to determinate the diagnostic yields of EBUS-TBNA, EUS-FNA and combined EBUS-TBNA and EUS-FNA modalities for nodal staging in potentially operable NSCLC patients. Therefore, we performed EBUS-TBNA after EUS-FNA in a single operation with different scopes and different endoscopists. All patients had a diagnosis of NSCLC before the procedure and none of them had a distant metastasis or inoperable T4 tumor which had been evaluated by thorax computed tomography (CT), F-18 fluorodeoxyglucose positron emission tomography with CT (PET-CT) or brain magnetic resonance imaging (MRI).

MATERIALS and METHODS

Patients

The present study was approved by the Ethics Review Board of Erciyes University and was supported by

Erciyes University Coordination Unit of Scientific Research Projects (TSG-2013-4704). Consecutive patients were prospectively enrolled in the study between March 2014 and November 2015. All patients had a potentially operable non-small-cell lung cancer diagnosis before endosonographic procedures. Distant metastasis or inoperable T4 disease was confirmed by CT scans of the chest, whole body integrated PET-CT scans, and brain MRI. We also excluded patients with poor medical conditions of grades 4 and 5 according to the American Society of Anesthesiologists Physical Status classification system. After staging with imaging modalities we included patients who had lymph nodes ≥ 10 mm on thorax CT or PET-CT positive lymph nodes (SUV-MAX ≥ 2.5) or centrally located lung tumor.

Anesthesia

The procedure was started with EUS. Patients were asked to fast before the procedure for 8 hours monitored. Continuous ECG, pulse oximetry, respiratory rate and intermittent venous blood pressure measurements were performed and the venous route was opened. EUS procedures were performed under conscious sedation anesthesia. Midazolam + fentanyl + propofol were administered with titration. During the procedure 3-4 L/min oxygen was administered via nasal cannula. Immediately after the EUS procedure without interruption, a laryngeal mask airway (LMA) was installed under general anesthesia and the bronchoscopists started the EBUS procedure. Anesthesia was induced with propofol and fentanyl, and neuromuscular blocking was done with rocuronium. Anesthesia was achieved with sevoflurane. Neuromuscular blockade was reversed by Sugammadex and the LMA was removed.

EBUS-TBNA Procedure and EUS-FNA Procedure

Endobronchial and endoscopic scopes were applied using the same device by replacing them in the same operation room. Endobronchial ultrasonography was conducted using a fiberoptic ultrasound bronchoscope (Convex Probe EBUS; BF-UC 160F-OL8; Olympus Medical Systems, Tokyo, Japan) and endosonographic ultrasonography was performed with a Convex Probe EUS (GF-UCT-180; Olympus Medical Systems, Tokyo, Japan). The location, shape, and structure of the lesions were examined with ultrasound. The locations of the stations were named and numbered using the lymph node map proposed by Mountain (9). After the bronchoscope and endoscope were guided to the target area, during real-time imaging a 22-gauge aspirating needle with a syringe connected proximally

(model NA-201SX-4022, Olympus for EBUS and model NA-220H-8022, Olympus for EUS) was pushed out from the distal tip of the scope and samples consisting of cells or tissue fragments were obtained. The aspirate was smeared onto glass slides, air dried and stained with Giemza. Histological cores were fixed with 10% neutral buffered formalin and stained with HE. Immunohistochemical staining was also performed when considered necessary. A rapid onsite cytopathological examination was not performed. Cytopathological specimens were categorized as (i) malignant (adequate sample with presence of malignant cells), (ii) reactive (sample consisting of mature lymphocytes and no malignant cells), (iii) anthracotic (sample consisting of mature lymphocytes, anthracosis and no malignant cells) (iv) inadequate (sample not consisting of mature lymphocytes). Malignant results were considered as positive; reactive, anthracotic and inadequate samples were considered as negative. We obtained two inadequate results by EUS-FNA and we did not exclude these results while calculating the sensitivity, negative predictive value or diagnostic accuracy of the procedure due to the low number of patients. We obtained no inadequate results by EBUS-TBNA.

Mediastinoscopy and Thoracotomy

In the present study, when one of the EBUS-TBNA and EUS-FNA cytopathologic results was positive, the results were assumed to be true positive and additional diagnostic procedures were not performed. However, if both of the cytopathologic results were negative, a cervical mediastinoscopy was performed.

Statistical Analysis

SPSS 15.0 software (SPSS, Chicago, Illinois, United States) was used for the basic statistical analysis. The Kolmogorov-Smirnov test was used to determine the normality of distributions of variables. Descriptive statistics are presented in frequency, percentage, mean, standard deviation, median, minimum and maximum values. Statistical analysis of the parametric variables between the 2 groups was performed using Student t-test. A p value of less than 0.05 was considered to be significant.

The diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of EBUS-TBNA were calculated as follows:

Sensitivity $[TP / (TP + FN)]$,

Specificity $[TN / (TN + FP)]$,

Positive predictive value $[TP / (TP + FP)]$,
 Negative predictive value $[TN / (TN + FN)]$,
 Diagnostic accuracy $[(TP + TN) / \text{total patients}]$
 (TP is true positive, FN is false negative, TN is true negative, and FP is false positive).

RESULTS

A total of 20 patients who had been diagnosed as NSCLC before endosonographic procedures were enrolled into the study. The demographic characteristics, NSCLC subtypes and lymph node characteristics are shown in Table 1.

Thirty lymph nodes were sampled by EBUS-TBNA and 17 lymph nodes were sampled by EUS-FNA in all 20 patients ($p < 0.05$). Because two patients had no visible lymph nodes which were easy to sample on EUS and one had hypoxemia at the procedure, 17 lymph nodes were sampled by EUS-TBNA in a total of 20 procedures (only one lymph node was sampled for each patient with EUS). The shortest diameters of the sampled

Table 2. Number and locations of lymph nodes targeted in endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and ultrasound-guided fine needle aspiration (EUS-FNA) (Values are number of nodes sampled).

Nodal stations	EBUS-TBNA, n (%)	EUS-FNA, n (%)
2R	1 (3.3)	-
4R	10 (33.3)	1 (5.9)
4L	3 (10.0)	5 (29.4)
7	14 (46.7)	11 (64.7)
11L	2 (6.7)	-
Total	30 (100)	17 (100)

lymph nodes were 11.9 ± 5.9 mm and 12.8 ± 5.9 mm on EBUS and EUS, respectively ($p > 0.05$). Each node underwent a median of 3 passes by EBUS-TBNA and 2 passes by EUS-TBNA ($p < 0.05$). Right lower paratracheal (station 4R) and subcarinal (station 7) lymph nodes were the most sampled stations with EBUS-TBNA and EUS-FNA, respectively (Table 2). One patient had hypoxemia during the EUS-FNA procedure which was improved with oxygen supplementation and no other major complications were observed with both modalities.

Figure 1 shows the diagnostic procedures step by step to the final pathological diagnosis. PET-CT was performed in all 20 patients. Seventeen had positive SUV uptake and three had benign SUV uptake. In these three benign nodal results by PET-CT, the final diagnosis was also negative by EBUS-TBNA, EUS-TBNA and also mediastinoscopy. Six of the 17 patients with positive SUV uptake on PET-CT had negative results by EBUS-TBNA, EUS-TBNA and also mediastinoscopy. One of the 17 patients whom had positive uptake at the N2 station and negative uptake at the N3 station had malignant result at N2 and also at N3 by EBUS-TBNA. Eleven patients had true positive results, six had false positive results and three had true negative results on PET-CT. The sensitivity, specificity, PPV, NPV and diagnostic accuracy of PET-CT were 100%, 33.3%, 64.7%, 100% and 70.0% respectively.

The final diagnosis was metastasis in 11 of 20 patients. In these 11 N2 metastatic patients, one also had N3 metastatic disease. Nine patients had metastatic N2 disease by EBUS-TBNA and one also had N3 metastasis. Nine patients had reactive and two patients

Number of patients, n	20
Age*, years	60.5 ± 7.8
Sex, n (%)	
Women	2 (10)
Men	18 (90)
Histologic types of tumors, n (%)	
Squamous cell carcinoma	11 (55)
Adenocarcinoma	8 (40)
Sarcomatoid carcinoma	1 (5)
Tumor location on CT, n (%)	
Right upper	10 (50)
Right middle	2 (10)
Right lower	4 (20)
Left Upper	1 (5)
Left Lower	3 (15)
Shortest diameter of lymph node*, mm	
EBUS	11.9 ± 5.9
EUS	12.8 ± 5.9
Number of passes, n (minimum-maximum)	
EBUS-TBNA	3 (1-5)
EUS-FNA	2 (1-3)

*Data presented as mean ± standard deviation.
 EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration.
 EUS-FNA: Endoscopic ultrasound-guided fine-needle aspiration.

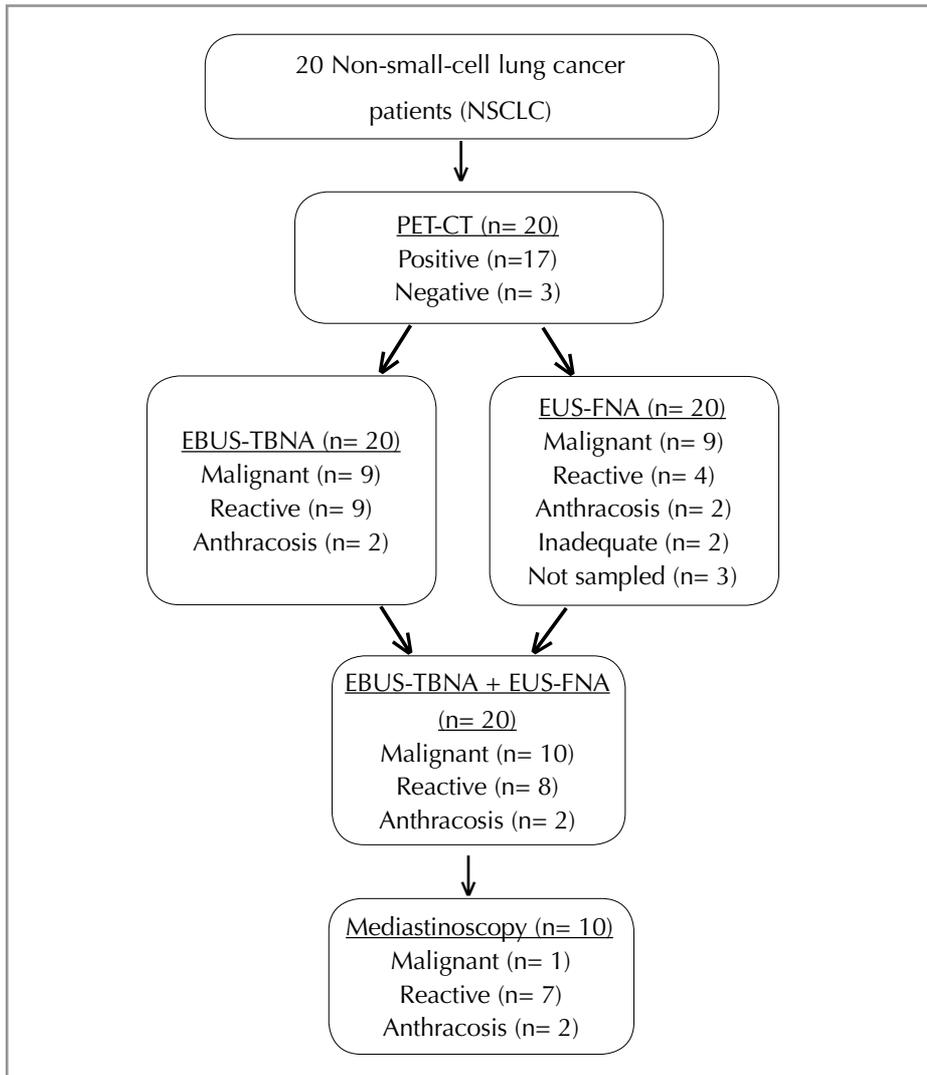


Figure 1. The diagnostic procedures step by step to the final pathological diagnosis.

Table 3. Results from F-18 fluorodeoxyglucose positron emission tomography with computed tomography (PET-CT), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) compared with the final diagnosis

	PET-CT (n= 20)	EBUS-TBNA (n= 20)	EUS-FNA (n= 17)	EBUS-TBNA + EUS-FNA (n= 20)
True positive, n (%)	11 (55)	9 (45)	9 (52.9)	10 (50)
True negative, n (%)	-	9 (45)	6 (35.3)	9 (45)
False positive, n (%)	6 (35)	-	-	-
False negative, n (%)	3 (15)	2 (10)	2 (11.8)	1 (5)
Sensitivity, %	100	81.8	81.8	90.9
Specificity, %	33.3	100	100	100
PPV, %	64.7	100	100	100
NPV, %	100	81.8	75	90
Diagnostic accuracy, %	70	90	88.2	95

PPV: Positive predictive value.
NPV: Negative predictive value.

had anthracotic lymph nodes by EBUS-TBNA. One of the two patients with reactive results by EBUS-TBNA had metastatic disease on EUS-FNA and the other one who also had a negative result on EUS-FNA had metastatic nodal disease by mediastinoscopy. Seventeen of the 20 patients were sampled by EUS-FNA. Nine patients also had metastatic N2 disease by EUS-FNA. Four patients had reactive, two patients had anthracotic lymph nodes and two patients had inadequate samples. One patient with an inadequate result on EUS-FNA had metastatic N2 disease by EBUS-TBNA. One patient with a reactive result also had a reactive result by EBUS-TBNA, but the final diagnosis was metastatic disease on mediastinoscopy. The sensitivity, specificity, PPV, NPV and diagnostic accuracy of solely EBUS-TBNA and EUS-TBNA were 81.8%, 100%, 100%, 81.8% and 90%; 81.8%, 100%, 100%, 75% and 88.2% respectively. EBUS-TBNA and EUS-FNA had two false negative results separately. However, in both of these procedures one result classed as false negative by one procedure was classed as true positive by the other. Therefore, only one patient had a false negative result by combined EBUS-TBNA and EUS-FNA procedure in total 20 patients. When we look at the combined EBUS-TBNA and EUS-TBNA results, the sensitivity, specificity, PPV, NPV and diagnostic accuracy were 90.9%, 100%, 100%, 90.0% and 95.0%, respectively. Table 3 shows the results of diagnostic procedures.

Mediastinoscopy was performed for 10 patients and 9 of them had no metastatic nodal disease. Therefore, surgery was recommended for 9 patients. One of them did not agree to surgery so 8 patients underwent surgery. After surgery, nodal involvement was found to be same as in mediastinoscopy in these 8 patients. Therefore, we had no false negative results by mediastinoscopy.

DISCUSSION

The present study showed better sensitivity, NPV and diagnostic accuracy by combined EBUS-TBNA and EUS-FNA compared to the separate performance of these procedures while nodal staging in potentially operable NSCLC patients. Both of the procedures had two false negative results. However, one result classed as false negative by one procedure was classed as true positive by the other. Thus, performing the nodal staging by adding EUS-FNA to EBUS-TBNA prevented unnecessary mediastinoscopy in 1 (9.1%) of 11 nodal metastasis negative patients according to EBUS-TBNA

alone. In one of the first trials with EBUS-TBNA plus EUS-FNA, the NPV was 82%, 92% and 96% for endosonographic, endobronchial and combined procedures in suspected lung cancer patients (5). A recent meta-analysis with 1080 subjects showed significantly higher results by combined procedure compared to EBUS-TBNA alone which was similar to our results (10). In spite of the high diagnostic results by combined endosonographic procedure, all negative results must be confirmed by surgical methods such as mediastinoscopy (11). In our study we also confirmed our negative results by mediastinoscopy and one of the 10 patients with negative results by combined endosonographic procedures was found to have nodal metastatic disease at mediastinoscopy.

False positive results with imaging modalities remain problem especially in tuberculosis endemic countries (2,12). A report by Lee et al. compared the diagnostic yield of combined endosonographic methods with PET-CT (13). The result of the study showed that the specificity and diagnostic accuracy of the combined modalities were higher than with PET-CT at rates of 100% vs 37.5% and 100% vs 81%, respectively. Another important finding for their study is that the diagnostic accuracy was 100%, which is remarkable for these minimally invasive procedures. In the present study, when we compared the specificity and diagnostic accuracy of combined endosonographic modalities with PET-CT they were 100% vs 33.3% and 95% vs 70%, respectively. Although our diagnostic accuracy was not 100% , we also achieved results which resembled those in Lee's report.

Bronchoscopists or endoscopists can not sample all visible nodal stations because of the need to extend procedure time to do so and some accessibility problems. Therefore, they frequently sample only lymph nodes which seem malignant or easy to sample. So, evaluating and also sampling the mediastinal and hilar stations with different modalities make it easy to make a better diagnosis. Stations 8 and 9 can only be sampled by EUS, also, station 5 is easier to sample by EUS than by EBUS (14,15). Besides this, the easily sampled stations 2R and 4R by EBUS-TBNA can be seen with EUS; however sampling these stations is sometimes difficult because of their distant location (16,17). In a recent trial analyzing false negative results by EBUS-TBNA, EUS-FNA and combined procedure, the investigators found the false negative results of 23.8%, 28.6% and 14.7% per nodal station basis, respectively (18). The authors

explained the relatively higher negative results by the diagnostic reach of the techniques. We found no visible lymph nodes at stations 5, 8 and 9 in the subjects of the present study. In our report, one patient with a positive result by EBUS-TBNA at station 2R had a negative result at station 4L by EUS-FNA. At the same time, another patient with a positive result by EUS-FNA at station 4L had a negative result at station 4R. Therefore, our data also support the view that the EBUS-TBNA and EUS-FNA procedures complement each other for nodal sampling.

The sampled lymph node number (30 vs 17) and pass number (3 vs 2) were significantly higher in the EBUS group than in the EUS group. Although most of the reports sample almost an equal number of lymph nodes with EBUS and EUS, Hwangbo et al. reported more than 4 times the number of sampled lymph nodes by EBUS-TBNA than by EUS-FNA (15,19,20). There are some definitions for these difference such as accessibility or experience. We discussed the accessibility difficulties in the previous paragraph and besides this, we had limited experience in performing EUS-FNA for mediastinal nodal stations.

Both of the endosonographic procedures have low complication rates. Serious complications occur in EBUS-TBNA with a rate of 0.07% and in EUS-FNA with a rate of 0.14% (21,22). In the present study one patient had hypoxemia probably due to the anesthesia which was improved by oxygen supplementation.

In the present report the bronchoscopic and endoscopic procedures were performed by a pulmonologist and gastroenterologist with different scopes. Therefore, we did not perform EBUS as an EUS-bronchoscopy. We performed both procedures in the same operation room and with the same device but with different scopes, consecutively. This modality feel us safer across the pass laws when we met a complication.

Our study has some limitations. One of them was the low patient number. The other one was the low number of sampled lymph nodes and passes for EUS-FNA due to our limited experience and nodal accessibility problems.

In conclusion, although we have limited experience with combined endosonographic modalities we achieved 90% NPV and 95% diagnostic accuracy at staging mediastinal and hilar lymph nodes in poten-

tially operable NSCLC patients. Therefore, we think that EBUS-TBNA and EUS-FNA are complementary modalities for nodal staging in NSCLC patients.

REFERENCES

1. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, 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(5 Suppl):e211S-50S.*
2. Harders SW, Madsen HH, Hjorthaug K, Arveschoug AK, Rasmussen TR, Meldgaard P, et al. *Mediastinal staging in Non-Small-Cell Lung Carcinoma: computed tomography versus F-18-fluorodeoxyglucose positron-emission tomography and computed tomography. Cancer Imaging 2014;14:23.*
3. Toloza EM, Harpole L, McCrory DC. *Non-invasive staging of non-small cell lung cancer: a review of the current evidence. Chest 2003;123:137S-46S.*
4. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. *Preoperative mediastinal lymph node staging for non-small cell lung cancer: 2014 update of the 2007 ESTS guidelines. Transl Lung Cancer Res 2014;3:225-33.*
5. Herth FJ, Krasnik M, Kahn N, Eberhardt R, Ernst A. *Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. Chest 2010;138:790-4.*
6. Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, et al. *Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. JAMA 2010;304:2245-52.*
7. Berania I, Kazakov J, Khoreba M, Goudie E, Ferraro P, Thiffault V, et al. *Endoscopic Mediastinal Staging in Lung Cancer is Superior to "Gold Standard" Surgical Staging. Ann Thorac Surg 2016;101:547-50.*
8. Zhang R, Ying K, Shi L, Zhang L, Zhou L. *Combined endobronchial and endoscopic ultrasound-guided fine needle aspiration for mediastinal lymph node staging of lung cancer: a meta-analysis. Eur J Cancer 2013;49:1860-7.*
9. Mountain CF. *Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710-7.*
10. Dhooria S, Aggarwal AN, Gupta D, Behera D, Agarwal R. *Utility and Safety of Endoscopic Ultrasound With Bronchoscope-Guided Fine-Needle Aspiration in Mediastinal Lymph Node Sampling: Systematic Review and Meta-Analysis. Respir Care 2015;60:1040-50.*
11. Colella S, Vilmann P, Konge L, Clementsen PF. *Endoscopic ultrasound in the diagnosis and staging of lung cancer. Endosc Ultrasound 2014;3:205-212.*

12. Ozgöl MA, Cetinkaya E, Tutar N, Ozgöl C, Onaran H, Bilaceroglu S. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy: A study in a tuberculosis-endemic country. *J Cancer Res Ther* 2013;9:416-21.
13. Lee KJ, Suh GY, Chung MP, Kim H, Kwon OJ, Han J, et al. Combined endobronchial and transesophageal approach of an ultrasound bronchoscope for mediastinal staging of lung cancer. *PLoS One* 2014;9:e91893.
14. Dietrich CF, Annema JT, Clementsen P, Cui XW, Borst MM, Jansen C. Ultrasound techniques in the evaluation of the mediastinum, part I: endoscopic ultrasound(EUS), endobronchial ultrasound (EBUS) and transcutaneous mediastinal ultrasound (TMUS), introduction into ultrasound techniques. *Thorac Dis* 2015;7:E311-25.
15. Tournoy KG, De Ryck F, Vanwalleghem LR, Vermassen F, Praet M, Aerts JG, et al. Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer: a randomized trial. *Am J Respir Crit Care Med* 2008;177:531-535.
16. Kramer H, van Putten JWG, Douma WR, Smidt AA, van Dullemenb HM, Groena HJM. Technical description of endoscopic ultrasonography with fine-needle aspiration for the staging of lung cancer. *Respir Med* 2005;99:179-185.
17. Hwangbo B, Lee GK, Lee HS, Lim KY, Lee SH, Kim HY, et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. *Chest* 2010;138:795-802.
18. Talebian Yazdi M, Egberts J, Schinkelshoek MS, Wolterbeek R, Nabers J, Venmans BJ, et al. Endosonography for lung cancer staging: predictors for false-negative outcomes. *Lung Cancer* 2015;90:451-6.
19. Herth FJ, Lunn W, Eberhardt R, Becker HD, Ernst A. Transbronchial versus transesophageal ultrasound-guided aspiration of enlarged mediastinal lymph nodes. *Am J Respir Crit Care Med* 2005;171:1164-7.
20. Ohnishi R, Yasuda I, Kato T, Tanaka T, Kaneko Y, Suzuki T, et al. Combined endobronchial and endoscopic ultrasound guided fine needle aspiration for mediastinal nodal staging of lung cancer. *Endoscopy* 2011;43:1082-9.
21. Eapen GA, Shah AM, Lei X, Jimenez CA, Morice RC, Yarmus L, et al. Complications, consequences, and practice patterns of endobronchial ultrasound-guided transbronchial needle aspiration: Results of the AQuIRE registry. *Chest* 2013;14:1044-1053.
22. von Bartheld MB, van Breda A, Annema JT. Complication rate of endosonography (endobronchial and endoscopic ultrasound): a systematic review. *Respiration* 2014;87:343-51.