Value of endobronchial ultrasound in staging non-small cell lung cancer

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ÖZET

Küçük hücreli dışı akciğer kanserinin evrelendirilmesinde endobronşiyal ultrasonun yeri

Endobronşiyal ultrason rehberliğinde ince iğne aspirasyonu (EBUS-TBİA), mediastinal lenfadenopatilerin değerlendirilmesinde doğru sonuç veren, güvenli ve minimal invazive bir tekniktir. Çalışmamızın amacı; tek kanallı bronkoskop kullanarak EBUS probunun katkısını ortaya koymaktır. Çalışmaya kanıtlanmış akciğer kanseri tanısı olan ve toraks bilgisayarlı tomografisinde genişlemiş (kısa aksı > 1 cm) mediastinal lenf nodu olduğu için EBUS-TBİA yapılan 22 hasta retrospektif olarak dahil edildi. Hastaların ortalama yaşı 56.8 ± 9.0 (45-76) olup, hepsi erkekti. Örneklenen 32 lenf nodunun ortalama büyüklüğü 19.9 ± 6.5 mm (10-30) idi. Ortalama örneklem sayısı 3.2 ± 0.9 (1-5) idi. Yeterli materyal lenf nodlarının 31 (%97)'inde elde edildi. On beş (%68.1) olguda lenf nodu metastazı tespit edildi. Negatif sitolojik sonuca ulaşılan 7 olguda mediastinoskopi uygulandı. Bir olgudaki minimal hemoraji dışında komplikasyon gözlenmedi. EBUS-TBİA'nın duyarlılığı %88.2, özgüllüğü %100, doğruluğu %90.9 olarak bulundu. Sonuç olarak; mediastinal lenf nodlarının EBUS rehberliğinde TBİA'sı küçük hücreli dışı akciğer kanserinde yüksek yeterlilik ve tanı oranı sağlayan güvenli bir araçtır.

Anahtar Kelimeler: *Endobronşiyal ultrason, akciğer kanseri, evreleme, transbronşiyal iğne aspirasyonu.*

SUMMARY

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Endobronchial ultrasound guided fine-needle aspiration (EBUS-TBNA) is an accurate, safe and minimally invasive technique for the analysis of mediastinal lymph nodes. The aim of our study was to assess the value of EBUS probe using single-channel bronchoscope. Twenty-two patients who underwent EBUS-TBNA with proven non-small cell lung cancer and enlarged (> 1 cm) mediastinal lymph node at chest computed tomography were retrospectively enrolled in the study. The mean age of the patients was 56.8 ± 9.0 (45-76), and all of them were men. Mean size of sampled 32 lymph nodes was 19.9 ± 6.5 mm (10-30). The average number of needle passes was 3.2 ± 0.9 (1-5). Adequate material was found in 31 (97%) of the lymph nodes. In 15 (68.1%) of the patients lymph node metastasis was detected. Of 7 patients with negative cytology, a mediastinoscopy was done. There were no complications other than minimal hemorrhage. The sensitivity of EBUS-TBNA was calculated as 88.2%, whereas the specificity was 100% and accuracy was found to be 90.9%. EBUS guided TBNA of mediastinal lymph nodes is a safe approach which can be a tool for obtaining adequate material and high diagnostic yield in staging of non-small cell lung cancer.

Key Words: *Endobronchial ultrasound, lung cancer, staging, transbronchial needle aspiration.*

Accurate staging of the mediastinum in lung cancer is essential for optimizing treatment strategies transbronchial needle aspiration (TBNA) is a well-established bronchoscopic technique (1,2). Conventional TBNA is a blind procedure. The accuracy for TBNA varies widely in the literature (i.e. 20 to 89%) (3,4). Important factors that can influence the results of TBNA are established lymph node enlargement on computed tomography (CT), the lymph node size, site of the lymph node, the kind of needle used, number of aspirates performed, the ability and the experience of the operators, and the availability of rapid on site evaluation (ROSE) (5). Recently, there has been significant interest in imaging-assisted TBNA. Procedure guidance with the help of CT fluoroscopy, as well as endobronchial ultrasound (EBUS), has been shown to be feasible and simple to perform (6-8). Those studies suggested a significant increase in yield. In a previously published study, it was shown that endobronchial ultrasound (EBUS) with TBNA was highly accurate in staging the mediastinum in patients with non-small cell lung cancer (9). This study was designed to address the question of whether EBUS-guided TBNA can decrease the need of mediastinoscopy.

MATERIALS and METHODS

Between October 2006 and June 2007, a total of 22 patients with cytologically-proven non-small cell lung cancer who had enlarged mediastinal lymph nodes without any distant metastases and were referred for conventional TBNA evaluation of mediastinal lesions were evaluated by EBUS-TBNA. Patient selection was based on CT findings showing mediastinal lymph node enlargement (> 1 cm in short-axis dimension). Lymph node status was classified according to the international staging system reported by Mountain and Dressler (10). To be included in this study, patients were required to have a mediastinal lymph node accesible by EBUS-TBNA with a short diameter of 10 to 30 mm on axial chest CT. Informed consent was obtained from all patients. All the prospectively recorded data were evaluated retrospectively. It is a retrospective study without disclosure of patients identities and our institutional review board approwal has been waived.

Bronchoscopy was performed in standard fashion under local anesthesia using xylocaine (maximum 8 mg/kg) and conscious sedation using midazolam (0.07-0.1 mg/kg; maximum 5 mg) for flexible endoscopy. All EBUS-TBNA procedures were performed as described below. Lymph node size on chest CT scan, number of passes, diagnosis, and complications were recorded. A positive result was either a specific diagnosis (e.g. malignant cells) or a lymphocyte-positive specimen, indicating sampling of the lymph node was successfully achieved. All patients with negative result underwent a surgical

biopsy procedure (mediastinoscopy or surgical mediastinal lymph node dissection).

EBUS

EBUS technique, using a radial probe (RP) with a rotating transducer at the distal tip, which produces a 360° image to the long axis of the bronchoscope was used. Through a bronchoscope with 2.8-mm working channel (Pentax EB 1970 and Olympus Excera and Olympus p 40D; Olympus; Tokyo, Japan), a flexible ultrasound probe with a 20-MHz transducer (UM-BS 20-26 R Olympus ultrasonic probe with driving unit MH-240 and processor EU-M 30s; Olympus) was introduced. The probe was placed through a guide sheath in the working channel of the bronchoscope (11,12). The probe was positioned near the target area, where a balloon surrounding the probe has to be inflated with water in order to ensure coupling with the airway wall and transmission of the ultrasound waves. The probe was used to visualize the lesion. The exact location of the target lymph nodes and their relation to the tracheobronchial tree were noted. Once the target lymph node was identified the probe then was removed from the working channel, and the needle is placed through the sheath and remains in place to stabilize the lesion during the TBNA (7,13). Consequently, the actual TBNA procedure was performed without real-time needle monitoring.

TBNA

TBNA was performed as previously described before (2-4). Only cytology specimens were obtained with a dedicated 22-gauge needles (MW 522; Bard; Billerica, MA). The "hub against the wall" and "cough" methods were used for all puncture (2). The aspirated material was expelled onto glass slides and specimens were air-dried on site before being sent to the pathology department. No on-site cytology was used.

Statistical Analysis

SPSS 11.5 system was used. Chi-square and Fisher tests were used to compare diagnostic ratios. $p< 0.05$ was accepted significant. The sensitivity, specificity, and accuracy of the EBUS-TBNA were calculated using the standard definition.

RESULTS

EBUS-TBNA was used to sample 32 lymph nodes [fourteen in station 7, sixteen in station 4R, and two in station 10R from 22 patients (all men; mean age, 56.8 ± 9.0 years)] were examined (Table 1,2). The mean lymph node size was 19.9 ± 6.5 mm (range, 1.0 to 3.0 cm) in short-axis diameter. The average number of aspirations was 3.18 ± 0.95. The material was diagnostic in twenty nine (91%) of the 32 lymph node stations. No diagnostic difference was detected between subcarinal lymph nodes compared with the other lymph nodes ($p> 0.05$).

A significant relationship between lymph node size and presence of metastasis was found (Table 3) ($p= 0.003$). Mean diameter of 29 lymph nodes with diagnostic result was 20.24 ± 6.56 mm whereas mean diameter of the lymph nodes without metastasis was 16.67 ± 5.77 mm. There was no statistically significant relationship (p=

Table 1. Localizations, sizes, sampling numbers and results of the lymph nodes.

Localization	n	Mean lymph node diameter in CT (mm)	Malignant aspirate in lymph node (n, %)	Diagnostic lymph node (n, %)	Mean sampling number (n)
Paratracheal	16 (50%)	18.0 ± 6.53 (10-30)	8 (50%)	13 (81.3%)	3.31 ± 0.95 (2-5)
Subcarinal	14 (43.8%)	22.07 ± 6.46 (12-30)	11 (78.6%)	14 (100%)	3.0 ± 1.04 (1-5)
Hilar	2 (6.3%)	20.0 ± 0.0 (20-20)	1 (50.0%)	2 (100.0%)	3.0 ± 0.0 (3-3)
Total	32	19.91 ± 6.49 (10-30)	20 (62.5%)	29 (90.63%)	3.18 ± 0.95 (1-5)

Table 2. Characteristics of the patients and their lymph nodes.

	Age	Localization	Size	Number of sampling	Diagnosis with EBUS-TBNA
1	54	Paratracheal	20	2	-
2	65	Right paratracheal	20	4	+
3	76	Subcarinal	12	2	-
		Precarinal	12	4	-
		Right lower paratracheal	10	3	-
4	50	Right paratracheal	30	5	+
5	56	Subcarinal	30	3	+
		Lower paratracheal	10	3	-
6	49	Left lower paratracheal	10	4	-
7	46	Subcarinal	25	3	+
8	55	Subcarinal	20	2	+
		Precarinal	30	1	+
		Paratracheal	20	2	+
9	57	Right lower paratracheal	30	4	-
10	71	Subcarinal	30	2	+
11	48	Right lower paratracheal	18	2	+
12	71	Right hilar	20	3	-
		Right lower paratracheal	20	3	-
		Subcarinal	20	3	-
13	62	Subcarinal	20	5	+
14	51	Subcarinal	30	3	+
15	68	Right lower paratracheal	10	3	-
16	49	Right lower paratracheal	10	4	-
17	51	Subcarinal	20	3	+
18	56	Right hilar	20	3	+
		Right upper paratracheal	20	3	+
		Right lower paratracheal	20	3	+
19	45	Subcarinal	20	3	+
20	65	Subcarinal	25	4	+
21	48	Right upper paratracheal	20	5	+
		Right lower paratracheal	20	3	+
22	57	Subcarinal	15	4	+

+: Malign cells seen, -: No malign cells seen.

0.4). Of 22 patients with lymph node metastasis, 15 (68.2%) had right-sided tumor, whereas 7 (31.8%) had left-sided non-small cell lung cancer. There was no statistically significant relationship between side of tumor and lymph node involvement (p= 0.63).

Mediastinal or hilar metastasis was confirmed by EBUS-TBNA in 15 (68.1%) of the cases. A positive EBUS-TBNA result was considered a true positive because the chance of contamination is rare. All patients with negative result underwent a surgical biopsy procedure. In seven patients, EBUS-TBNA cytology from lymph nodes were negative for malignancy. Of these, subsequent surgical staging (mediastinoscopy) did not reveal any malignant lymph node involvement in 5

Table 3. Relation of lymph node size and detection rate of malignancy.

n= 32	n	Mean size (mm)
Nonmalign	12	15.33 ± 6.51
Malign	20	22.65 ± 4.80

n: Number of lymph nodes, p= 0.003.

(22.7%) patients. In two cases, a mediastinal lymph node involvement was disclosed by mediastinoscopy (Table 4).

As complication, a minimal hemorrhage was observed in one patient,during the procedure. The sensitivity, specificity, accuracy, negative predictive and false negative values were 88.2%, 100%, 90.9%, 71.4%, and 28.6%, respectively.

DISCUSSION

EBUS-TBNA is a well-established bronchoscopic technique but remains underutilized, and the yield varies widely (14). This fact may be due to the long learning curve. Additionally, conventional TBNA is a fairly blind technique preventing target visualization. For this reason, obtaining adequate material from small lymph nodes are difficult. Several improvements exist in order to improve the yield. Important factors that can influence the results of TBNA are established; lymph node enlargement on CT, the lymph node size, site of the lymph node, the type of dedicated needle, number of aspirates performed, the ability and the experience of the operators, and the availability of ROSE (5). The most commonly recommended is ROSE and, recently, the number of aspirations (up to seven)(15). ROSE is not available at all institutions and it is costly (16). Also, multiple aspirations from a nodal target is time-consuming and increases the chance of damaging the bronchoscope.

Table 4. Comparison of TBNA results with mediastinoscopy.

n= 22	Mdx (+)	Mdx (-)	Total
Dx (+)	15 (88.2%)	0	15 (68.2%)
Dx (-)	2 (11.8%)	5 (100%)	7 (31.8%)
Total	17	5	22

Dx: Diagnosis, Mdx: Mediastinoscopy.

EBUS offers a unique way of imaging airways and parabronchial structures during a bronchoscopy procedure (17-19). The procedure is safe, minimally invasive, and it does not require general anesthesia or hospitalization (18,19). The complication rate is extremely low nearly next to nil (8,17,18,20). No complications, either related to the procedure, other than minimal hemorrhage in one case, were observed in our study.

Several studies have been conducted using EBUS-TBNA for the localization of mediastinal nodes. In a prospective study of 242 patients with enlarged mediastinal nodes (mean diameter 1.7 cm) at chest CT, all target nodes could be identified by EBUS, independently size or location. Adequate samples were obtained in 86% of cases and malignant lymph node involvement was assessed in 72% of cases (7). In our study, all target nodes were identified, adequate samples were obtained from 31 lymph node (91%) but from all cases (100%).

A randomized trial of the use of EBUS in the guidance of TBNA procedures has been reported before (23). In the study done by Shannon, no significant difference was found between EBUS guidance and conventional TBNA. In that study, ROSE was also used in all patients, potentially masking any benefit of image guidance. On the other hand, another large (n= 200) randomized trial done by Herth et al., it was demonstrated that, EBUS guidance significantly increased the yield of TBNA in all stations (84% versus 58%) (22). In our study significant increase was obtained by EBUS guidance. In one study, adequate lymph node sampling was obtained from 59 out of 60 patients (98%) and a diagnosis is made in 45 of 60 patients (75%) (24). In our study, adequate lymph node sampling was done in all patients (100%) and accuracy was calculated as 90.9%.

Herth et al. showed that, EBUS guidance significantly increased the yield except in the subcarinal region (86 versus 74%) (22). However, there was no difference related to localization of the lymph nodes. This could be attributable to relatively smaller sample size of our study.

In our study, a lymph node involvement was detected in 15 cases. Despite the potential usability of EBUS-TBNA technique the rate of false-negativity remained not ignorable. In patients with negative results an invasive staging procedure such as mediastinoscopy prior to definitive surgery should be done. In our study, seven patients with negative EBUS-TBNA underwent a surgical staging procedure (mediastinoscopy). Of these, the final diagnosis was positive in two patients (40%). In a series done by Rintoul et al., it was shown that, EBUS-TBNA avoided the need for a staging procedure in 11 cases from a total of 20 cases (25). Our results were smilar to the results reported earlier by other authors using radial or linear probes (21).

In conclusion, we found that, EBUS-TBNA was an accurate tool for staging. It can be considered a routine adjunct to bronchoscopy before more invasive procedures such as mediastinoscopy directly.

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