

The utility of endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal or hilar lymph node evaluation in extrathoracic malignancy: Benign or malignant?

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Abstract:

OBJECTIVE: Newly arising enlarged or hypermetabolic mediastinal/hilar lymph nodes (LNs) in patients with previously diagnosed extrathoracic malignancies raise suspicion of metastasis. Relatively high proportion of these LNs is due to a benign condition. We aimed to determine frequency of malignant LNs and role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for clarification of the origin of suspicious LNs in these patients.

METHODS: Consecutive patients with a known extrathoracic malignancy and suspected hilar/mediastinal LN were included in this prospective study. Computed tomography (CT) of thorax and positron emission tomography-CT of all patients were taken. LNs with short axis >1 cm at CT of thorax and SUV \geq 2.5 were accepted suspicious for malignancy. All patients underwent EBUS-TBNA for pathological verification of LNs. Patients with benign diagnosis either underwent invasive procedures or were followed up. The results were evaluated for frequency of malignant hilar/mediastinal LNs and sensitivity, specificity, and diagnostic values of EBUS-TBNA.

RESULTS: A total of 48 cases with a mean age of 57.4 ± 11.6 were included. All cases had the diagnosis of an extrathoracic malignancy. 78 LNs were aspirated with EBUS-TBNA in 48 cases (1.62 LNs/patient). The mean short axis of aspirated LNs was 1.51 ± 0.63 . Results of EBUS-TBNA revealed malignancy in 15 cases (31.2%), tuberculosis in six cases (12.5%), sarcoidosis in four cases (8.3%), and reactive adenitis in 23 cases (48%). The sensitivity, specificity, and negative predictive value of EBUS-TBNA for malignancy were 83.3%, 100%, and 90.9%, respectively. When both benign and malignant diseases were considered, sensitivity, specificity, negative predictive value, and diagnostic accuracy of EBUS-TBNA were 89.2%, 100%, 86.9%, and 93.7%, respectively.

CONCLUSIONS: The ratio of benign LNs in patients with extrathoracic malignancies is relatively high. EBUS-TBNA is a safe, minimally invasive, and effective method for clarification of intrathoracic LNs.

Key words:

Endobronchial ultrasound, extrathoracic malignancy, fine needle aspiration, lymph nodes, mediastinal diseases

Accurate diagnosis of enlarged hilar and mediastinal lymph nodes (LNs) is mandatory for adequate management of patients with a known primary malignancy. Many mediastinal or hilar LNs in patients with previously diagnosed extrathoracic malignancy are not malignant and benign conditions such as tuberculosis or sarcoidosis may be the diagnosis in some patients; therefore, histopathologic confirmation is mandatory.^[1]

Computed tomography (CT) is generally the initial tool for assessing mediastinal LN enlargement. Radiologically, the LNs are considered abnormal when the short-axis diameter is more than 10 mm.

However, the accuracy of CT in mediastinal evaluation is of limited value. Positron emission tomography-CT (PET-CT) offers higher efficacy in diagnosing mediastinal lymphadenopathies. Still, tissue sampling is necessary to achieve the accurate cytohistological or pathological diagnosis. Although mediastinoscopy is still the gold standard, it is costly, difficult to reach, and is associated with higher morbidity and mortality.^[2-4] Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technique offering pathological diagnosis of mediastinal and hilar LNs. This technique allows real-time ultrasound localization and aspiration of hilar

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and mediastinal LNs. EBUS-TBNA offers an effective, safe and accurate, minimally invasive strategy for evaluating pathological hilar and mediastinal LNs. However, negative findings require surgical evaluation such as mediastinoscopy. The role of EBUS-TBNA in staging the mediastinum in lung cancer and diagnosing granulomatous diseases such as tuberculosis or sarcoidosis have been previously studied. However, mediastinal or hilar LN evaluation by EBUS-TBNA in patients with extrathoracic malignancies still needs further investigation. When mediastinal or hilar lymphadenopathy accompanies an extrathoracic malignancy, accurate LN sampling is necessary for optimal diagnosis, staging, and treatment. We aimed to determine the role of EBUS-TBNA for clarification of the nature of enlarged hilar and/or mediastinal LNs in patients with known extrathoracic malignancy.

Methods

All patients with a known extrathoracic malignancy who had undergone EBUS-TBNA for assessment of enlarged and hypermetabolic hilar and/or mediastinal LNs between December 2008 and June 2011 were reviewed. Our primary endpoint was to determine the etiology and prevalence of malignancy for hypermetabolic and enlarged hilar/mediastinal LNs in patients with a previously diagnosed extrapulmonary malignancy during the oncologic follow-up period and the diagnostic yield of EBUS-TBNA in these LNs. The study was conducted at a tertiary hospital and with a catchment area of 2 520 km² and a population of approximately 2 000 000. Forty-eight patients who underwent EBUS-TBNA were included in the study. Forty-six patients were operated at the time of first diagnosis of extrathoracic malignancy and all patients were under local and systemic control up to the last PET-CT examination. The patient's clinical stage when the extrathoracic malignancy was first diagnosed was not taken into consideration. The hypermetabolic LNs became evident at the patient's follow up by an oncologist. EBUS-TBNA was performed within 10 days after PET-CT examination. Written informed consent was provided from all patients. The study protocol was approved by the Local Institutional Ethics Committee.

Demographic data, sites of primary malignancies, radiological and PET-CT findings, EBUS findings, stations of aspirated LNs, cytological findings and diagnoses, and final diagnoses were recorded.

Computerized tomography was performed in all patients with a multislice scanner (Toshiba, Asteion Super 4 slice CT; Japan). One hundred milliliters of intravenous contrast iohexol, 350 mg/ml iodine (Omnipaque, GE Healthcare, Waukesha, WI) were given prior to imaging. LNs with a short-axis greater than 1 cm were considered as pathological.

Patients had PET-CT scans as a part of their routine oncological evaluation. An experienced nuclear medicine physician evaluated the PET images. 18-Fluorodeoxyglucose PET-CT was considered positive if the PET-CT report stated that there was hypermetabolic activity with a standardized uptake value ≥ 2.5 consistent with malignant disease.

All EBUS-TBNA procedures were performed by two experienced bronchoscopists. Following sedation with midazolam, the

patient was intubated orally with an EBUS-guided TBNA bronchoscope (7.5 MHz, BF-UC160F; Olympus Optical Co. Tokyo, Japan). Mediastinal and hilar LNs were examined systematically, using Mountain's system,^[5] and measured. The short and long axis of each visualized LN was recorded and LNs with Fluorodeoxyglucose (FDG) uptake ≥ 2.5 SUV max were aspirated with dedicated 22 gauge needles (NA-201SX-4022-C; Olympus Tokyo, Japan). At least three passes in each LN were performed. The aspirated material was smeared on glass slides and the remaining specimen was fixed in 90% alcohol. Both air-dried and alcohol-fixed slides were prepared for each LN and sent to the laboratory for cytopathological evaluation. On-site examination was not performed. On cytopathological examination, the puncture was considered adequate when lymphocytes were seen in the smear. EBUS-TBNA results were considered malignant when the aspirated material contained malignant cells. A diagnosis of tuberculosis or sarcoidosis was made based on cytopathology that showed the presence of caseating or noncaseating granuloma, in addition to clinical, radiological, and microbiological findings. Any diagnosis other than malignancy required further investigation such as mediastinoscopy or thoracoscopy or radiologic follow-up on the outcome of the LNs for at least 6 months. On follow-up, LNs that persisted in size, diminished, or resolved were considered benign.

The sensitivity, specificity, negative predictive value, and diagnostic accuracy of EBUS-TBNA were calculated based on the final diagnoses of enlarged and hypermetabolic mediastinal and/or hilar LNs. The distribution of malignant or non-malignant causes of these LNs was evaluated.

Statistical analyses were performed using SPSS 17.0 package program. The sensitivity and specificity were calculated using the standard definitions. A *P* value less than 0.05 was considered statistically significant.

Results

The mean age of 12 male (25%) and 36 female (75%) patients was 57.4 ± 11.6 years. All patients had been previously diagnosed with an extrathoracic malignancy. The most common previously diagnosed disease was breast carcinoma (45.8%), followed by gastrointestinal malignancy (22.9%) and genitourinary malignancy (20.8%). One patient had both breast and cervical cancer and another patient had both colon and renal cell carcinoma. The types of malignancies are shown in Table 1.

The mean standardized uptake value of sampled LNs was 11.1 ± 5.4 (2.5-22.2) in PET-CT. A total of 78 LNs were sampled. The mean number of LN stations sampled per patient was 1.62. At least three aspirations were performed for each LN. Hilar (station 10 or 11) nodes were aspirated in seven (14.6%) patients and mediastinal (stations 2, 4, 7) nodes in 31 (64.6%) patients. In 10 (20.8%) patients, both hilar and mediastinal nodes were sampled. The stations of the LNs aspirated by EBUS-TBNA are shown in Table 2. The mean short-axis of aspirated mediastinal LNs was 1.51 ± 0.63 (0.50-4.00) cm. All LN samples contained adequate material.

Results of EBUS-TBNA revealed malignancy in 15 (31.2%) cases, tuberculosis in six (12.5%) cases, sarcoidosis in four

(8.3%) cases, and reactive adenitis in 23 (47.9%) cases. The flow diagram of patients enrolled in the study is shown in Figure 1. Fourteen of 33 cases who were diagnosed as nonmalignant by EBUS-TBNA underwent mediastinoscopy and the rest were followed radiologically for at least six months. At the end of the follow-up period, the LNs that were diagnosed as sarcoidosis or reactive adenitis by EBUS-TBNA and were stationary decreased in size or disappeared were considered benign. Patients who were diagnosed as tuberculosis and received anti-tuberculosis therapy for 6 months had resolution or a decrease in size of their LNs. As a final diagnosis, malignancy was detected in 18 cases, tuberculosis in six cases, sarcoidosis in four cases, and reactive adenitis in 20 cases [Table 3].

Of 48 cases with a confirmed extrapulmonary malignancy, only 18 (37.5%) were found to have a malignancy in recently arising mediastinal or hilar LNs. The majority of the study population was diagnosed with granulomatous diseases (20.8%) or other benign conditions (41.6%). Procedure-related complications were minor bleeding in two cases and slight reversible oxygen desaturation in one case. No other complications were detected.

The sensitivity and specificity of EBUS-TBNA for malignancy was 83.3% and 100%, respectively. The negative predictive value for malignancy was 90.9%. When both benign and malignant diseases are considered, sensitivity, specificity, and negative predictive value and diagnostic accuracy of EBUS-TBNA were 89.2%, 100%, 86.9%, and 93.7%, respectively.

Discussion

Our primary endpoint was to determine the etiology and prevalence of malignancy for hypermetabolic and enlarged hilar/mediastinal LNs in patients with a previously diagnosed extrapulmonary malignancy during the oncologic follow-up period and the diagnostic yield of EBUS-TBNA in these LNs. We determined that in patients with a proven extrapulmonary malignancy, only 37.5% had malignancy in recently arising mediastinal or hilar pathologic LNs. Also, the sensitivity, specificity, and negative predictive value of EBUS-TBNA for malignancy were found to be 83.3%, 100%, and 90.9%, respectively. When all malignant and nonmalignant diseases were taken into consideration, the sensitivity, specificity, and negative predictive value were 89.2%, 100%, and 86.9%, respectively. The diagnostic accuracy of EBUS-TBNA was found to be 93.7%.

TBNA is a safe, minimally invasive, and repeatable technique for mediastinal LN sampling. However, since it is a blind method, it has a moderate diagnostic yield. Its utility can be improved with guidance by endoscopic or endobronchial ultrasonography.^[4,6] Yasufuku *et al.* reported the sensitivity, specificity, and negative predictive value of EBUS-TBNA as 94.6%, 100%, and 89.5%, respectively. The accuracy was 96.3%.^[7] In a more recent study, EBUS-TBNA was found to have better diagnostic yield, with 95% sensitivity, 100% specificity, 93% negative predictive value, and 97% accuracy.^[8]

Endoscopic ultrasound (EUS) is another potential minimally invasive and inexpensive alternative for mediastinal LN sampling. To date, studies have shown that EBUS-TBNA has

higher diagnostic yield in comparison to EUS-guided fine needle aspiration (EUS-FNA).^[9,10] One possible explanation for this is that EBUS allows access to a higher number of LNs.

Mediastinoscopy is the gold standard for mediastinal LN sampling, with 80 to 85% sensitivity, 89% negative predictive value, and 100% positive predictive value. However, it is an invasive procedure necessitating general anesthesia, hospital admission, and higher cost. Although generally safe, it still has the potential risks of major morbidity and mortality. Moreover,

Table 1: The distribution of previously diagnosed malignancies in patients with newly arising mediastinal and/or hilar lymph nodes

Malignancy	Frequency (n)	Percentage (%)
Breast carcinoma	22	45.8
Colon carcinoma	7	14.5
Cervix carcinoma	4	8.3
Gastric carcinoma	3	6.2
Renal cell carcinoma	4	8.3
Lymphoma	2	4.2
Endometrium carcinoma	2	4.2
Malignant melanoma	2	4.2
Laryngeal carcinoma	2	4.2
Thyroid carcinoma	1	2.1
Pancreatic carcinoma	1	2.1

Table 2: The sites of lymph nodes sampled by EBUS-TBNA

Lymph node	Number of cases	Percentage (%)
2R	3	6.2
2L	2	4.2
4R	28	58.3
4L	21	43.8
7	1	2.1
10R	11	22.9
10L	6	12.5
11R	6	12.5

EBUS-TBNA = Endobronchial ultrasound guided transbronchial needle aspiration; R = right; L = left

Table 3: Comparison of EBUS-TBNA results and final diagnosis in patients with known extrathoracic malignancies

Diagnosis	Final diagnosis		EBUS-TBNA	
	n	%	n	%
Malignancy	18	37.5	15	31.2
Breast	10	20.8	8	16.7
Colon	1	2.1	1	2.1
Gastric	2	4.2	1	2.1
Renal	2	4.2	2	4.2
Endometrium	1	2.1	1	2.1
Malignant melanoma	1	2.1	1	2.1
Pancreas	1	2.1	1	2.1
Tuberculosis	6	12.5	6	12.5
Sarcoidosis	4	8.3	4	8.3
Reactive adenitis	20	41.6	23	48

EBUS-TBNA = Endobronchial ultrasound guided transbronchial needle aspiration

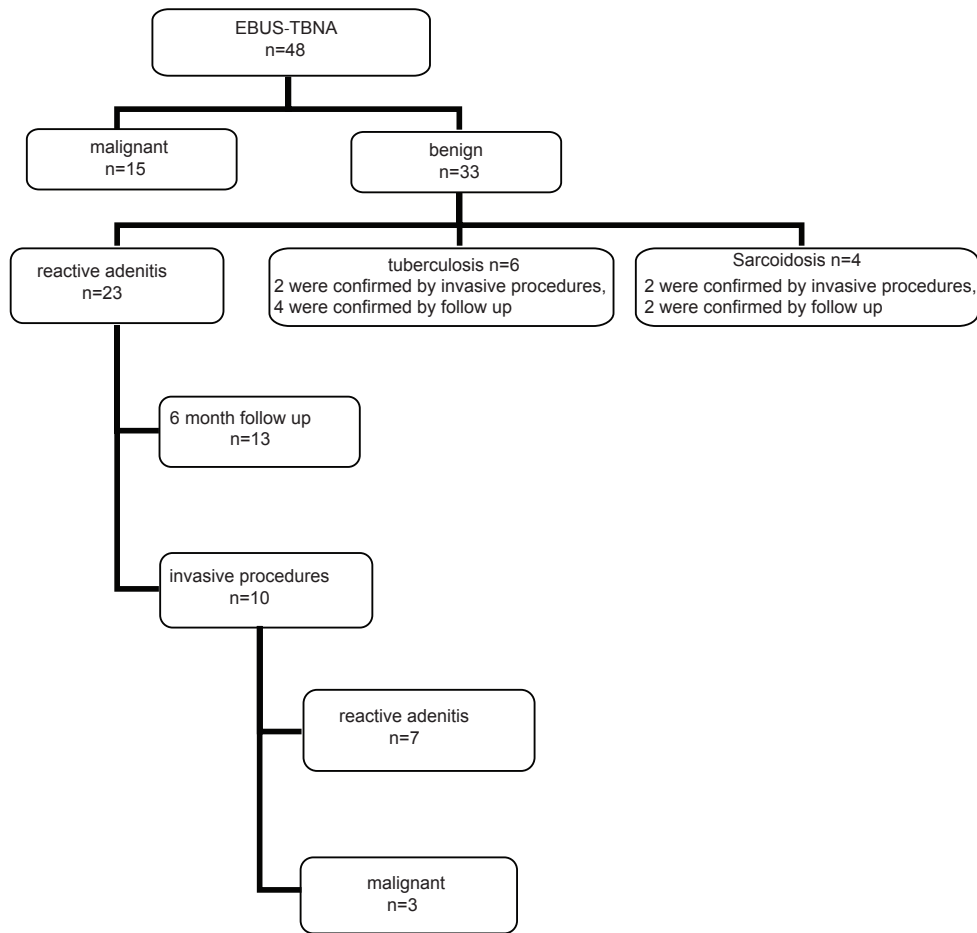


Figure 1: The flow diagram of patients enrolled in the study

it is limited in accessing the aortopulmonary window and posterior subcarinal and hilar regions. EBUS, on the other hand, allows access to posterior the subcarinal and hilar regions. It can safely be done as an outpatient procedure, carries much lower morbidity, and can easily be repeated if necessary.^[4,8,9]

In a prior report about the role of EBUS-TBNA in diagnosing mediastinal or hilar LNs in cases with extrapulmonary malignancies, EBUS-TBNA was found to have a sensitivity, accuracy, and negative predictive value of 88%, 93%, and 85%, respectively.^[11] A relatively high (38.6%) number of cases were confirmed to have benign diagnoses.

Park *et al.* evaluated mediastinal LNs in 39 patients with extrathoracic malignancy and 20 patients with no known primary malignancy. The most common sites of primary malignancies in their study population were colon, liver, kidney, and breast. They included cases who underwent EBUS-TBNA for suspected mediastinal LN metastases according to CT findings (short axis larger than 1 cm) or PET-CT results. They found that 40 of the 59 patients were found to have mediastinal metastases using any diagnostic tool. EBUS-TBNA findings indicated that 34 of the 59 patients were positive for malignancy. They reported that the EBUS-TBNA sensitivity and specificity for the detection of mediastinal malignancy in patients with a previous extrathoracic malignancy were 96.3% and 100%, respectively, and 61.5% and 100% in patients without

a previously diagnosed malignancy. The overall sensitivity and specificity were 81.0% and 100%, respectively.^[12]

Tournoy *et al.* analyzed 92 patients with extrathoracic malignancy with a suspicion of mediastinal or hilar spread, who underwent EBUS-TBNA. The majority of the study population (nearly 70%) had head and neck carcinomas, colorectal carcinomas, and renal cell carcinomas; 73% had PET-CT scans and 97% of these showed positive FDG uptake. As a final diagnosis, 29 cases had benign conditions (reactive adenopathy, sarcoidosis, silicosis, and hamartoma). They reported the sensitivity and negative predictive value of EBUS in detecting mediastinal spread of extrathoracic malignancies as 85% and 76%, respectively.^[13] In a multicenter study, intrathoracic LN metastases from an extrathoracic malignancy were evaluated by EBUS-TBNA. EBUS-TBNA was found to have 87% sensitivity, 73% negative predictive value for malignancy, and 88% overall accuracy. This analysis concluded that EBUS-TBNA diagnosed mediastinal or hilar metastases in 44% of the patients, new lung cancer in 12% of the patients, and sarcoidosis in 9% of the patients.^[14] In our study, we diagnosed mediastinal or hilar LN metastasis in 31.2% of the patients but we did not detect any new lung cancer.

In our study, the most common previously diagnosed primary malignancies were breast carcinoma, followed by gastrointestinal malignancies and genitourinary malignancies.

Park *et al.* reported that the most common sites of primary malignancies in their study population were colon, liver, kidney, and breast, respectively.^[12] In the study of Tournoy *et al.*, head and neck carcinomas were the most common primary malignancies followed by colorectal carcinomas and renal cell carcinomas.^[13] In our study, all EBUS-TBNA performed LNs were hypermetabolic at PET-CT. In the study of Tournoy *et al.*, PET scan was available only in 73% of cases (positive in 97%), while in the other patients the size of the LN or just the presence of the lung lesion explained the clinical suspicion for metastasis.^[13]

Consistent with previous reports, our findings demonstrate similar diagnostic accuracy of EBUS-TBNA for detection of malignant LNs. The sensitivity and specificity for detecting malignancy in our study was 83.3% and 100%, respectively. Another important finding in our study is the high prevalence of benign conditions involving mediastinal or hilar LNs in patients with confirmed malignancies and the diagnostic value of EBUS-TBNA in these diseases. For granulomatous diseases (six tuberculosis and four sarcoidosis), the diagnostic accuracy and sensitivity were 100%. In a patient with a confirmed malignancy, a recent onset of a LN is often thought to be metastasis; however, granulomatous inflammation or other benign conditions are ultimately diagnosed in many cases. Tuberculosis accounts for an important number of cases in areas where the prevalence of tuberculosis is high (i.e., 30/100 000 in Turkey).^[15] Without definitive histopathological confirmation, many LNs in cancer patients may be falsely attributed to recurrence of malignancy and unnecessary toxic treatments may be administered. Therefore, definitive tissue diagnosis is mandatory to consider a LN metastatic.

We conclude that it must be kept in mind that not all newly occurring LNs in cancer patients are malignant. Benign conditions constitute to a relatively high percentage of the final diagnoses of these lymphadenopathies. EBUS is a safe, minimally invasive, and accurate procedure for diagnosing mediastinal or hilar lymphadenopathy in patients with known extrathoracic malignancy. Nevertheless, due to the possibility of underdiagnosis, an invasive technique is indicated when the results are negative.

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