Med Ultrason 2018, *Vol. 20, no. 2, 154-158*
DOI: 10.11152/mu-1282

Differentiating metastatic lymph nodes in lung cancer patients based on endobronchial ultrasonography features

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Abstract

Aim: The aim of this study was to identify easy and relatively effective ultrasound criteria for metastatic mediastinal lymph node prediction. **Materials and methods:** A retrospective chart review of patients who underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from March 2014 to September 2016 was performed. We used the following EBUS sonographic features for metastatic lymph node prediction: 1) length of the short axis, 2) shape, 3) margin, 4) echogenicity, 5) central hilar structure, and 6) coagulation necrosis sign. These sonographic findings were compared with the final pathology results or clinical follow-up. **Results:** A total of 227 lymph nodes were retrospectively evaluated in 133 lung cancer patients; 72% of the lymph nodes had been proven to be malignant metastasis. Logistic regression analysis revealed that the length of the short axis, shape, margin, and echogenicity were independent predictive factors for metastasis. We developed a sum score based on these four sonographic features. A larger sum score trended toward a greater possibility of malignancy. If all four predictive factors were preserved, the diagnostic accuracy, the value of the specificity and the positive predictive value of the sonographic feature would be higher than 90%. **Conclusions:** The sonographic features of EBUS are valuable tools in predicting metastatic lymph nodes in lung cancer patients.

Keywords: endobronchial ultrasound-guided transbronchial needle aspiration; lung cancer; mediastinal lymph node

Introduction

Lung cancer is the most common cause of cancer-related death worldwide [1]. Accurate diagnosis of metastasis to the mediastinal and hilar lymph nodes is essential not only to evaluate the prognosis but also to devise an appropriate treatment plan [2]. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a relatively new and minimally invasive procedure for mediastinal and hilar lymphadenopathy staging. Prior study has shown that it has greater diagnostic accuracy than currently available imaging tools, including computed tomography (CT) and positron emission tomography [3]. Because of its ability to provide adequate pathologic specimens, some experts also recommend that EBUS-TBNA be used as a diagnostic investigation for patients with suspected lung cancer [4-6].

Several lymph nodes are frequently detected in the same station. Distinguishing the most likely target lesion is a critical issue for lung cancer staging during EBUS-TBNA. A retrospective study reported that 4 sonographic features (round shape, distinct margin, heterogeneous echogenicity, presence of a coagulation necrosis sign) are useful in evaluating metastatic lymph nodes in lung cancer patients [7]. New imaging patterns (presence of matting, non-hilar vascular pattern perfusion) are also used to predict lymph node metastasis [8]. Pulmonary physicians need more experience to familiarize themselves with the increasing number of sonographic features, and

Received 16.10.2017 Accepted 02.01.2018
Med Ultrason
2018, Vol. 20, No 2, 154-158
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also need a prolonged period of examination. Hence, our aim in this study was to identify simple and relatively effective ultrasound criteria for predicting thoracic lymph node metastasis in lung cancer patients.

Materials and methods

This study was approved by the National Taiwan University Hospital Institutional Review Board (IRB #201708033RINC). Informed consent was waived as existing data were analyzed in a de-identified manner for this study.

Participants

We performed a retrospective chart review of lung cancer patients with mediastinal lymphadenopathy who underwent EBUS-TBNA at the Department of Thoracic Medicine, National Taiwan University Hospital, and National Taiwan University Hospital, Hsin-Chu branch from March 2014 to September 2016. Patient data on age, gender, and indications for EBUS-TBNA were collected. The locations of the lymph nodes that we approached were recorded using the international TNM staging system reported by Mountain et al [9].

EBUS-TBNA

EBUS-TBNA was performed with the patients under consciousness sedation with intravenous fenatyl and midazolam, in a bronchoscopy room setting. At least one of the experienced pulmonary physicians (CKL, LYC, CCH) performed the procedure assisted by two to three pulmonary fellow doctors or dedicated technicians. A real-time ultrasound biopsy bronchoscope (BF-UC260FW; Olympus; Tokyo, Japan), and a dedicated 22-gauge needle (NA-201SX-4022; Olympus) were used for TBNA biopsies. Rapid on-site cytology exam was not performed for all of our patients due to the lack of availability in our clinical setting. When several lymph nodes existed together, a sequential N3-N2-N1 strategy was followed for lymph node staging.

In patients with malignancy, the diagnosis was determined on the basis of malignant cytological and/or histological results at EBUS-TBNA or with surgical-pathological confirmation. In patients with benign processes, the diagnosis was confirmed by surgical biopsy, or with at least 6 months of radiological and clinical follow-up.

EBUS imaging characteristics of lymph nodes

Based on a previous report by Fujiwara [7], we selected the following EBUS sonographic features: 1) length of the short axis (≥1 cm or <1 cm); 2) shape (round or non-round); 3) margin (distinct or indistinct); 4) echogenicity (heterogeneous or homogeneous); 5) central hilar structure (CHS), presence or absence; and 6) coagulation necrosis sign (CNS), presence or absence. Round shape was defined as lymph nodes with a ratio of the short to long axis of less than 1.5. If the ratio was more than 1.5, or the lymph nodes had other irregular shapes (such as a triangular shape), we classified them as non-round. Distinct margin was represented as the majority of the margin (>50%) visualized with a high echoic border. Heterogeneous echogenicity presented as several hypoechoic spots within the lymph nodes. When a linear, flat, hyperechoic area was detected within the center of the lymph node, we named it a central hilar structure. A coagulation necrosis sign was a hypoechoic area within the lymph node without blood flow.

Statistical analysis

All six sonographic characteristics of the lymph nodes were compared with the final cytological and/or pathologic result of the lymph node. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy rate were calculated via standard definitions. Significance was considered for a p-value of less than 0.05. We used SPSS version 22.0 (IBM, SPSS, Chicago, IL) for statistical analysis.

Results

Patients and mediastinal lymph nodes

The demographic characteristics of the 133 patients who were enrolled and evaluated in this study are summarized in Table I. A total of 227 mediastinal and hilar lymph nodes were analyzed. Table II summarizes the EBUS-TBNA characteristics and the proportion of each station during the period. No patients had major complications related to EBUS-TBNA, except minimal self-limited wound oozing during the procedure.

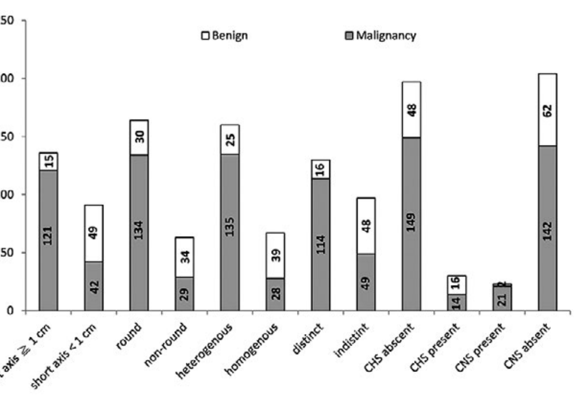

Fig 1. The sonographic features of EBUS classification and final confirmation based on pathologic results or clinical follow-up for at least 6 months via chest CT. The white bar shows the number of benign lymph nodes and the gray bar represents the metastatic lymph nodes. CHS- central hilar structure; CNS -coagulation necrosis sign.

Table I. Patient Characteristics

Patient characteristics	N
Patients	133
Age, y, mean (range)	65.2 (33-89)
Male (%)	84 (63.2)
Indication (%)	
Suspected lung cancer with mediastinal lymphadenopathy for diagnosing	89 (66.9)
For lung cancer staging	26 (19.5)
Suspected disease progression for re-biopsy	18 (13.5)
Underlying lung cancer (%)	
Adenocarcinoma	88 (66.2)
Squamous cell carcinoma	24 (18.0)
Small cell carcinoma	15 (11.3)
Adenosquamous carcinoma	2 (1.5)
Mixed NSCLC and small cell carcinoma	1 (0.8)
Other NSCLC	3 (2.3)

N – number of patients;NSCLC – non-small cell lung cancer.

Table II. Mediastinal and hilar lymph nodes characteristics

LN characteristics	N
Number	227
Size (mm, range)	14.4 (4.0-38.9)
Puncture times (range)	2.9 (1-5)
Malignancy (%)	163 (71.8)
Location (%)	
2R	10 (4.4)
2L	0 (0)
4R	84 (37.0)
4L	34 (15.0)
7	52 (22.9)
10R	8 (3.5)
10L	3 (1.3)
11R	20 (8.8)
11L	16 (7.0)

LN – Lymph node; N – number of patients

Table III. Univariate and multivariate analysis of the sonographic features for predicting metastatic lymph nodes

Morphologic category	Univariate p value	Multivariate p value	Odds Ratio (95% CI)
Short axis	<0.001*	<0.001*	9.411 (4.784-18.512)
Shape	<0.001*	<0.001*	5.237 (2.777-9.874)
Echogenicity	<0.001*	<0.001*	7.521 (3.941-14.356)
Margin	<0.001*	<0.001*	6.980 (3.617-13.469)
Absence of CHS	0.001*	0.741	3.548 (1.614-7.798)
CNS	0.028*	0.760	4.585 (1.043-20.155)

CHS – central hilar structure; CNS – coagulation necrosis sign; * – statistical significance with p-value < 0.05

Table IV. Diagnostic yield of sonographic features and sum scores for predicting metastatic lymph nodes

Morphologic category	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic yield (%)
Short axis	74.2	76.6	89.0	53.9	89.0
Shape	79.8	53.1	81.7	50.0	74.0
Echogenicity	82.8	60.9	84.4	58.2	76.7
Margin	69.9	75.0	87.7	49.5	71.4
Sum score of sonographic features for malignancy prediction					
1	9.2	61.0	37.5	20.9	37.5
2	17.2	78.1	66.7	27.0	66.7
3	26.4	89.1	86.0	32.2	86.0
4	46.6	95.3	96.2	41.2	96.2
Non sonographic features for benign prediction					
0	23.4	99.4	93.8	76.8	93.8
EBUS-TBNA	90.8	100.0	100.0	77.5	93.4

EBUS-TBNA – endobronchial ultrasound-guided transbronchialneedle aspiration, PPV – positive predictive value; NPV – negative predictive value

Sonographic features of EBUS

When the following sonographic characteristics presented in the lymph nodes: short axis greater than 1 cm, round shape, distinct margin, heterogeneous echogenicity, absence of CHS, or presence of CNS, they were suspected to be metastatic lymph nodes (fig 1). Logistic regression analysis revealed that the length of the short axis, shape, margin, and echogenicity were independent predictive factors (Table III). The odds ratios for the four predictive factors were 9.41, 5.24, 7.52, and 6.98, respectively.

To investigate a method for evaluating the possibility of metastatic lymph nodes in lung cancer patients, we developed a model of sum scores, in which the number of positive independent predictive factors is counted. A higher positive predictive value and diagnostic accuracy for predicting malignancy was obtained if a larger sum score was calculated (Table IV). If all four independent predictive factors coexisted, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 46.3%, 95.3%, 96.2%, 41.2%, and 96.2%, respectively. Compared to the EBUS-TBNA, the diagnostic accuracy rate was 93.4%. The sensitivity, specificity, positive predictive value, and negative predictive value were 92.8%, 100%, 100%, 83.3%, respectively. In classifying non-independent predictive factors that were "benign", the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 23.4%, 99.4%, 93.8%, 76.8%, and 93.8%, respectively.

Discussions

In the present study, length of the short axis, shape, margin, and echogenicity were good sonographic features for predicting thoracic lymph node metastasis in lung cancer patients. Larger sum scores tended to indicate a greater possibility of malignancy. If all of these four predictive factors were preserved, the diagnostic accuracy, value of specificity and positive predictive value of the sonographic feature would be higher than 90%.

Malignant metastasis induces an increased density of tumor cells and vascular structures within the lymph nodes, and soon after expands the shape and size of the lymph node [10]. Based on cancer behavior, fibrosis, necrosis, hemorrhage and cavitation will then occur [11]. These features are consistent with our EBUS finding that malignant lymph nodes will expand to a larger and rounder shape. Heterogeneous echogenicity means that non-unique components exist in the structure of the lymph nodes. A hyperechoic margin presents because of a hypercellular area relative to the nearby normal tissue [11]. These behaviors are consistent with previous studies. Fujiwara et al reported that a round shape, distinct margin and heterogeneous echogenicity can differentiate malignancy from reactive lymph nodes [7]. Wang et al reported that a long axis and round shape were two independent predictors for metastasis [8]. Schmid-Bindert et al found that echogenicity had a really high sensitivity, specificity, along with positive and negative predictive values for evaluating lung cancer metastasis [12].

The CHS is the lymphatic sinus within the lymph node. When cancer cells infiltrate the sinus, the hilum will become blurred [13]. CHS has been used as a benign predictor, but was not applied in our study. In the present study, 14 lymph nodes with CHS were proved to have malignant cells. A large proportion of lesions (57.1%, 8/14) had a short axis less than 1 cm. This finding suggests that the CHS may still be preserved in the early stage of metastasis. CNS is an ultrasound finding indicating that central necrosis is present in the lesions. Fujuwara et al reported that the CNS is frequently seen in malignancy [7], although other studies did not show the same results. One report even found that the CNS is an auxiliary sign for differentiating tuberculosis [14]. In the present study, the CNS was indeed frequently detected in malignant lymph nodes; however, most of them were large in size. In all, 91.1% (21/23) of lymph nodes contained a CNS with a short axis longer than 1 cm, and 73.9% (17/23) had one longer than 1.5 cm. CNS is supposed to be a non-specific sign for large lesions with central necrosis.

Grouped lymph nodes have often been detected in the same station during systemic lung cancer staging. Determining the highest likelihood of metastatic lymphadenopathy is an important mission. In prior studies, a target lesion with more predictive factors would have a higher potential to be malignant. [8] We used four simple criteria (size, shape, margin and echogenicity) in the present study to calculate the sum score. The chance of malignancy in a lymph node becomes greater if a larger sum score is obtained. If all four criteria exist, the diagnostic accuracy and positive predictive value of the sonographic feature will be very similar to that of EBUS-TBNA. If a single lymph node with no sonographic criteria is detected during staging, should we only look at the morphology without doing the biopsy? Many experts advise that the answer is no. We should always try to get tissue diagnosis during systemic cancer staging. Otherwise, we can utilize the high positive predictive value to predict a benign process (93.8%) when the target lesion lacks sonographic criteria for malignancy. In this situation, true negative is more credible when our cytologic or pathologic reports reveal only benign lymphocytes. Instead of repeat EBUS-TBNA or surgical biopsy, imaging follow-up may be selected first.

Some reports have revealed new imaging patterns via EBUS, such as matting, calcification, a vascular pattern, and nodal conglomeration, which may be used to distinguish between malignancy and benign process [8]. More imaging criteria can be more time-consuming during the procedure, and require more training for young bronchoscopists. We believe the fewer imaging criteria with EBUS in our study will require less time to achieve accuracy. New ultrasound imaging modalities during EBUS, such as elastography and spectrum analysis of EBUS radiofrequency may offer more information for predicting malignancy [15-17]. However, neither of these modalities are available in our hospital.

Our study has some limitations. First, we focused only on lymphadenopathy in patients with underlying lung cancer. Their sonographic features most likely differ from those of lymph nodes in patients with noncancerous disease, such as tuberculosis or sarcoidosis. Therefore, our study results can be applied only in situations of lung cancer staging. Applications in other conditions should be cautiously interpreted. Second, we did not perform EBUS-TBNA for all the mediastinal lymph nodes in each patient. Grouped lymph nodes often are detected in the same station during systemic staging. We chose the target site in which metastatic lymph nodes were most likely. However, this may be closer to real-world practice, in that only one to two lymph nodes within one station are sampled. Third, we did not use a surgical criteria standard in defining all final pathologies of the patients, even though most benign processes were clinically followed for at least 6 months and characterized via chest CT. Finally, this was a retrospective study. A prospective study is warranted to confirm the utility of sonographic features in exploring metastatic lymph nodes.

Conclusion

This study showed that the sonographic features of EBUS are valuable tools for predicting metastatic lymph nodes in lung cancer patients. The lymph node characteristics of a short axis of less than 1 cm, round shape, distinct margin, and heterogeneous echogenicity are independent predictive factors. If we sum the number of these four factors that are present, larger scores will trend toward a higher likelihood of malignancy. Compared to recent studies, fewer imaging patterns were used in the present study, but the diagnostic accuracy was still acceptable. We believe the use of our sum score is more suitable for clinical practice.

Conflict of interests: none

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