

# Predictors of malignancy in EUS-guided FNA for mediastinal lymphadenopathy in patients without history of lung cancer

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## Abstract:

**BACKGROUND:** Mediastinal lymphadenopathy (ML) poses a great diagnostic challenge.

**OBJECTIVE:** To investigate the predictors of malignancy in endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) of ML in patients without known lung cancer.

**DESIGN:** Retrospective study.

**SETTING:** Tertiary referral center.

**METHODS:** One hundred eight patients without known lung cancer who underwent EUS guided-FNA for ML between 2000 and 2007. All subjects underwent EUS-guided FNA. Data was collected on patients' demographics, and lymph node (LN) characteristics. Diagnosis of LN malignancy was based on FNA findings and clinical follow-up.

**RESULTS:** One hundred eight patients were analyzed; 58 (54%) were men and 87 (79%) were Caucasian. Mean age was 55 years. Prior malignancy was present in 48 (43%) patients. A total of 126 FNA samples from 126 distinct LNs were performed. Twenty-five (20%) LNs were positive for malignancy. Mean short and long-axis for LNs were 13 and 29 mms respectively. Round shape and sharp borders were found in 29 (15%) and 25 (22%) LNs, correspondingly. Independent predictors of a malignant FNA were: Prior cancer (OR 13.10; 95% CI 2.7-63.32;  $P = 0.001$ ), short axis (OR 1.10; 95% CI 1.00-1.22;  $P = 0.041$ ) and sharp LN borders (OR 5.47; 95% CI 1.01-29.51;  $P = 0.048$ ). Age, race, gender, long axis, round shape were not associated with cancer in our cohort.

**LIMITATIONS:** Retrospective design and lack of surgical gold standard.

**CONCLUSIONS:** Increased risk of malignancy was associated with prior history of cancer, larger LN short axis and presence of LN sharp borders. These predictors may help guide endoscopists perform FNA in malignant LNs, increasing the overall efficiency of EUS-FNA for ML.

## Key words:

Endoscopic ultrasound, lung cancer, mediastinal lymphadenopathy, staging, fine needle aspiration

Mediastinal lymphadenopathy (ML) is nowadays increasingly seen by gastroenterologists given the gradual acceptance of endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) for the evaluation of enlarged mediastinal nodes. The management and prognosis of patients with ML vary tremendously according to its etiology. Thus, differentiating inflammatory processes from malignancy is not only key for treatment decisions but also vital in predicting survival.<sup>[1,2]</sup>

Classic endosonographic features of malignant lymph node (LN) invasion such as hypoechoic appearance, sharply demarcated borders, rounded contour, and size greater than 10 mm have been previously described by Catalano *et al.*<sup>[3]</sup> using data from patients with esophageal cancer. Later, Buthani *et al.*<sup>[4]</sup> re-evaluated those features and also the role of EUS-FNA in patients with lung, esophageal, and pancreatic cancer, showing that FNA increases the accuracy of

EUS. Chen and Eloubeidi<sup>[5]</sup> determined that, if all echofeatures were present in mediastinal or periintestinal LNs, the change of malignancy was higher than 80%. Later, the same criteria have been proved to be accurate in patients with known lung cancer, with FNA significantly increasing its accuracy.<sup>[6]</sup> However, the endosonographic features of malignant mediastinal LN invasion in patients with ML without known lung cancer have not been studied. Therefore, we sought to evaluate the clinical and endosonographic predictors of malignancy in EUS-guided FNA and validate the predictive accuracy of the number of classic lymph node malignant echofeatures among patients with ML without history of lung cancer.

## Methods

### Study population

After obtaining Institutional Review Board approval of the University of Alabama at

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Birmingham, data from patients with CT documented ML who underwent EUS-guided FNA between September 2000 and May 2007 were retrospectively reviewed. Of the 119 patients initially included in the study, we excluded 6 due to a prior history of lung cancer and 5 due to missing data. This resulted in a study population of 108 (90%) subjects.

### EUS-guided FNA

EUS was performed under conscious sedation by a single experienced endosonographer (M.A.E.) with greater than 10 000 EUS procedure overall experience as previously described,<sup>[1,7]</sup> who was aware of the presence of enlarged LN. A radial echoendoscope (GF-UM130, Olympus America, Melville, NY) was first used to evaluate the presence or absence of lymphadenopathy. The examination started by a full evaluation of the left adrenal gland by imaging it from the fundus of the stomach. The echoendoscope was then gradually withdrawn to evaluate the inferior pulmonary ligament nodal station (#9), the periesophageal areas (#8), the subcarinal space (#7) [Figure 1], the aortopulmonary window (#5) [Figure 2], and the upper and lower para-tracheal LNs (#2 and 4). Once a LN was identified, the radial echoendoscope was removed and a curvilinear echoendoscope (Olympus UC-30P or UCT 140) was then inserted and EUS-FNA of the target lesion(s) was performed as previously described<sup>[1,7]</sup> [Figure 3].

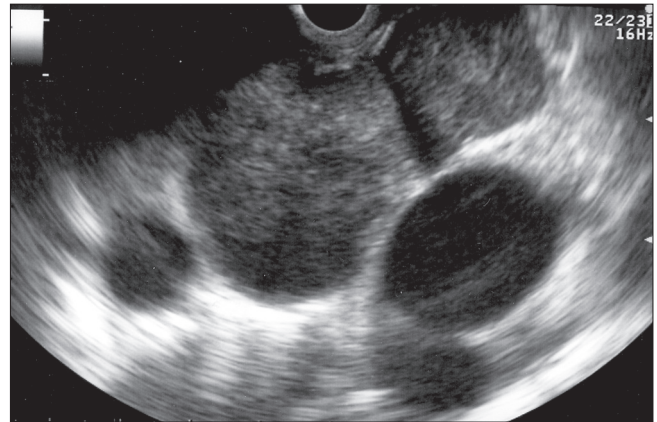
All EUS-FNAs were performed with 22-gauge adjustable-length Echotip needles (Wilson-Cook Inc, Winston-Salem, NC). However, since 2004, we have solely used the curvilinear echoendoscope since we felt that the radial echoendoscope was not adding to the management of the patients and most often FNA is performed. Cytologic diagnosis of the aspirated lesion was classified into four categories: (1) benign or reactive, (2) positive for malignancy, (3) atypical or suspicious for malignancy, or (4) nondiagnostic. The endosonographic criteria for malignant involvement of the LN were documented before cytologic evaluation as previously described.<sup>[3]</sup>

Diagnosis of LN malignancy was based on FNA findings and clinical follow-up data such as surgical specimens or unequivocal radiological findings of cancer progression. Patients were considered to have benign lymphadenopathy only if (1) the FNA was nonmalignant, (2) surgical and pathologic findings of the target LN from thoracotomy or other surgical procedure were benign, and (3) results of clinical and radiological 6-month follow-up were negative for malignancy at that LN station. If any of the above features was positive for malignancy, the target LN was considered to harbor malignancy.

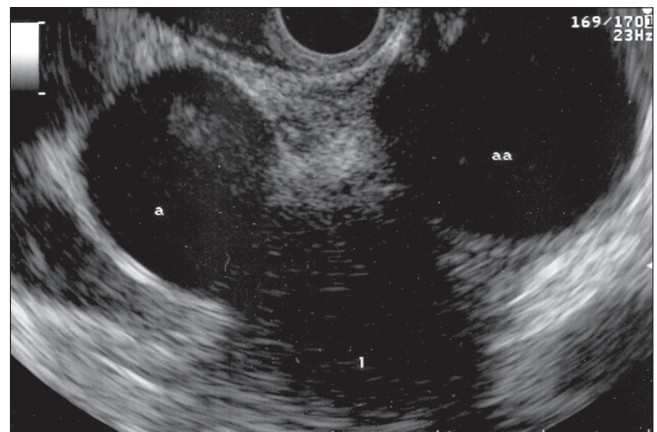
### Statistical analysis

Univariable comparisons between patients and lymph nodes with EUS-guided FNA finding positive and negative for malignancy were done using chi-square test for categorical variables and rank-sum test for continuous data. We used multinomial logistic regression to evaluate the predictors of FNA malignancy in multivariable analysis. We included patients' demographics such as age (in years), gender (male or female), race (Caucasian or African-American), and history of prior malignancy (yes or no) in our analyses. We also included the short and the long LN axis (in mm), LN echogenicity (hypoechoic or not), shape (round or not) and borders (sharp or not). The number of classic LN malignant features present was evaluated, including: Short axis  $\geq 10$  mm, sharp borders, hypoechoic appearance, and round shape. We used multinomial

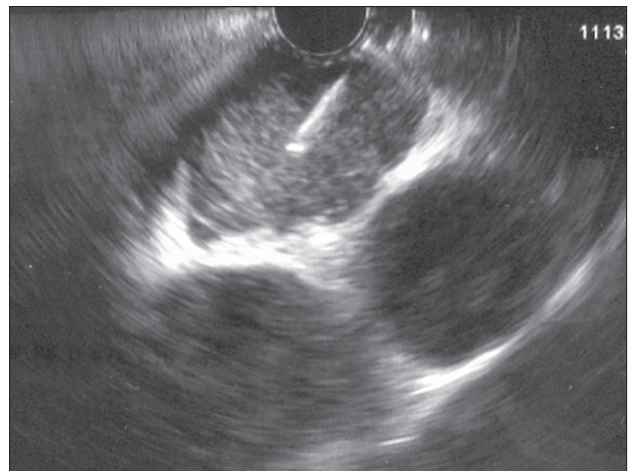
logistic regression to analyze the number of echofeatures and risk of malignancy. We also calculated the sensitivity, specificity, percentage of correctly classified patients according



**Figure 1:** EUS revealed enlarged bulky subcarinal lymph nodes (level 7). These lymph nodes are round, hypoechoic, and exhibited shape and distinct borders consistent with malignant involvement (UC 30 P Olympus echoendoscope scanning at 7 MHz)



**Figure 2:** EUS image of an enlarged aortopulmonary lymph node (level 5). The letters 'aa' denote aorta, and 'a' denotes pulmonary artery and 'l' denotes lymph node



**Figure 3:** EUS-guided fine needle aspiration of a subcarinal lymph node with a needle inside the lymph node

to the number of echofeatures and plotted a receiver operating characteristic (ROC) curve. All statistical analyses were performed using Stata 10 (StataCorp, College Station, TX) and R 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria). A  $P < 0.05$  was considered to indicate statistical significance.

## Results

Of the 108 patients included in the study and followed for a median time of 19 months, 58 (54%) were men and 87 (79%) were Caucasian. The median age was 55 years. History of prior malignancy was present in 48 (43%) patients. In univariable analysis, female gender ( $P = 0.018$ ) and previous history of malignancy ( $P < 0.001$ ) were associated with increased risk of positive FNA [Table 1].

A total of 126 FNA samples from 126 distinct LNs were analyzed. Twenty-five (20%) LNs were positive for malignancy. Cytology diagnosis and lymph node characteristics are shown in [Tables 2 and 3], respectively. The median short and long LN axes were respectively, 13 (range 2-42 mm) and 29 mm (range 8-60 mm). Round shape and sharp borders were found in 29 (15%) and 25 (22%) LNs, respectively. In univariable analysis,

**Table 1: Baseline patient characteristics**

Variables	Positive FNA no. (%)	Negative FNA no. (%)	P value
Total number of patients	23 (21)	85 (79)	-
Age (years)			0.170
Median (IQR)	63 (44-67)	55 (43-66)	
Ethnic group			0.570
White	17 (74)	68 (80)	
Black	6 (26)	17 (20)	
Gender			0.018
Male	7 (30)	51 (60)	
Female	16 (70)	34 (40)	
History of malignancy	19 (83)	27 (32)	<0.001
Prior procedure			-
None	22 (96)	66 (78)	
TBNA	0	8 (9)	
Mediastinoscopy	1 (4)	9 (11)	
CT-FNA	0 (0)	0 (0)	
Open biopsy	0 (0)	3 (4)	
Number of nodes sampled			0.617
1	21 (91)	70 (82)	
2	2 (9)	14 (17)	
3	0 (0)	1 (1)	

IQR = Interquartile range; FNA = Fine needle aspiration; TBNA = Transbronchial needle aspiration; CT-FNA = Computerized tomography-guided FNA

**Table 2: Final fine needle aspiration diagnosis**

Diagnosis	N	(%)
Benign lymph node	71	56
Granulomatous disease	30	24
Metastatic breast cancer	6	5
Non-Hodgkins lymphoma	5	4
Hodgkins lymphoma	2	1
Metastatic colon cancer	3	2
Other malignant	9	7

FNA positive for malignancy was associated with larger short axis ( $P = 0.003$ ), presence of round shape ( $P = 0.001$ ), sharp borders ( $P < 0.001$ ), and hypoechoic appearance ( $P = 0.022$ ). Long axis did not significantly correlate with FNA positivity ( $P = 0.293$ ; [Table 2]. A total of 85 LNs (78.7%) were located at level 7. Given the low number of LNs at other levels, we were not able to derive any meaningful conclusion on the association between LN location and risk of malignancy in our cohort.

In multivariable analysis, the significant independent predictors of malignancy in EUS-guided FNA were: Prior history of a cancer (odds ratio [OR] 13.10; 95% CI 2.71-63.32;  $P = 0.001$ ), short axis (OR 1.10; 95% CI 1.00-1.22;  $P = 0.041$ ) and presence of sharp LN borders (OR 5.47; 95% CI 1.01-29.51;  $P = 0.048$ ). Patient age, race and gender, long axis, and round shape were not independently associated with FNA positive for malignancy in our cohort [Table 4].

The number of classic echofeatures was significantly associated with risk of malignancy ( $P < 0.001$ ). We found that the risk of malignancy in LN with no classic echofeatures was 5% while the risk of malignancy was 75% in LN with all four echofeatures. Using the cut-off of two echofeatures or more, the sensitivity and specificity were, respectively, 67% and 77%. Three or more echofeatures yielded the highest percentage of correctly classified LN (83%) with a corresponding sensitivity and specificity of 52% and 92%, [Table 5]. The overall area under the ROC curve of echofeatures to predict LN malignancy was 0.767 [Figure 4].

**Table 3: Lymph node characteristics**

Variables	Positive FNA no. (%)	Negative FNA no. (%)	P value
Total number of nodes	25 (20)	101 (80)	-
Short axis			0.003
Median (IQR)	21 (12-25)	13 (9-17)	
Long axis			0.293
Median (IQR)	30 (27-41)	29 (18-37)	
Round shape	10 (40)	9 (9)	0.001
Sharp borders	12 (52)	13 (15)	<0.001
Hypoechoic appearance	15 (60)	33 (34)	0.022

IQR = Interquartile range; FNA = Fine needle aspiration

**Table 4: Multivariable predictors of positive EUS-guided fine needle aspiration**

Variables	OR	95% CI	P value
Patient age (years)	1.00	0.96-1.04	0.978
Ethnic group			
White	Ref	-	-
Black	0.92	0.22-4.00	0.920
Gender			
Male	Ref	-	-
Female	1.70	0.45-6.38	0.431
History of malignancy	13.10	2.71-63.32	0.001
Short axis (mm)	1.10	1.00-1.22	0.041
Long axis (mm)	1.01	0.94-1.08	0.849
Round shape	1.50	0.58-3.85	0.399
Sharp borders	5.47	1.01-29.51	0.048
Hypoechoic appearance	0.85	0.17-4.30	0.852

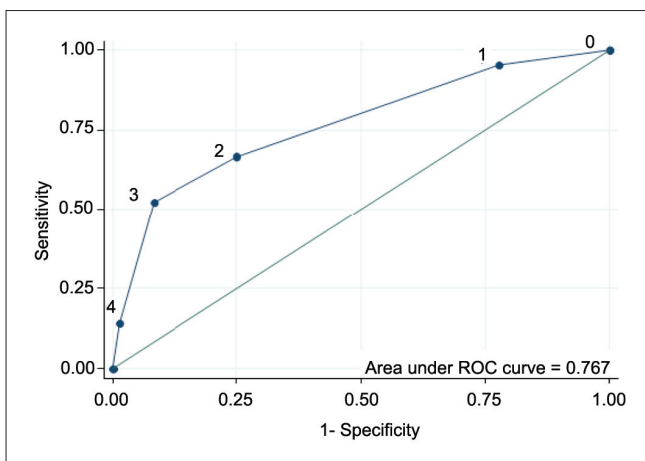


## Discussion

EUS was originally developed for local staging of gastrointestinal cancers but it also provides excellent access to the posterior mediastinum through the esophageal wall.<sup>[8]</sup> There have been several reports documenting that EUS-FNA is also useful to evaluate ML of unknown cause.<sup>[9-15]</sup> In some of these cases, lung cancer was suspected based upon imaging but no diagnosis had yet been made. In addition, some patients had a history of prior malignancy. Malignant lymphadenopathy was diagnosed by EUS-FNA in 42%-72% of cases.<sup>[9]</sup>

EUS-FNA is considered the diagnostic test of choice for evaluating ML. A recent meta-analysis showed that EUS-guided FNA has a high accuracy to diagnose malignancy in those patients. It has a sensitivity of 88.0%, specificity of 96.4%.<sup>[2]</sup> It is the preferred method for tissue sampling of such lesions in the subcarinal, subaortic (aortopulmonary window), lower paratracheal, and periesophageal stations found on cross-sectional imaging (CT, MRI, or PET).<sup>[9]</sup>

Classic EUS features of malignant LN invasion were initially described by Catalano *et al.* in a series which included 100 patients with esophageal carcinoma.<sup>[3]</sup> Echofeatures predictive of malignancy in increasing order of importance were (1) hypoechoic structure, (2) sharply demarcated borders, (3) round shape, and (4) size greater than 10 mm. Collectively, those features produced an additive effect with respect to accuracy in the prediction of malignant LN involvement; malignancy could be predicted with 100% accuracy when all four of the above were present.<sup>[3]</sup>



**Figure 4:** Receiver operator characteristic (ROC) curve for predicting malignant mediastinal lymphadenopathy according to the number of classic echofeatures of malignancy

Buthani *et al.*<sup>[4]</sup> re-evaluated endosonographic features of LNs assessing the utility of these features and of EUS-FNA in predicting malignant LN invasion. Thirty-five LNs in 25 patients with lung, esophageal, and pancreatic cancer were studied by EUS, of those, 21 LNs were of lung cancer patients. The four echofeatures of malignancy described by Catalano *et al.*<sup>[3]</sup> were compared between benign and malignant LNs. No single feature independently predicted malignant invasion. When all four of the above features were present in the same LN, the accuracy of predicting malignant invasion was 80%. However, all four features of malignant involvement were present in only 25% (4 of 16) of malignant LNs. The authors suggested that echofeatures may be a less reliable predictor of malignant invasion in pulmonary malignancies when compared to gastrointestinal cancers and concluded that EUS-FNA is needed for accurate LN assessment of malignancy in addition to evaluation of EUS features.

Chen and Eloubeidi<sup>[5]</sup> also demonstrated that EUS-FNA is more accurate than LN echofeatures alone. This study population included patients with mediastinal and perintestinal lymphadenopathy, in which 77% had a known primary malignancy, such as lymphoma, esophageal, lung or pancreatic cancer. In univariate analysis, mediastinal location and age were correlated with malignancy, as well as presence of at least two positive echofeatures. A larger dimension of the short axis was also associated with malignancy, a finding which is similar to our study and that also supports the concept that malignant LNs tend to be more round while benign ones more oval in shape. In multivariate analysis, number of LN echofeatures and advanced age of the patients were associated malignancy in EUS-FNA. EUS features were particularly unreliable in the mediastinum, when compared to EUS-FNA.<sup>[5]</sup>

Recently, Gleeson *et al.*<sup>[16]</sup> showed that hypoechoogenicity, short axis >6 mm or long axis >9 mm are independent predictors of malignancy in a population with untreated rectal cancer. In addition, Jamil *et al.*<sup>[17]</sup> displayed, in abstract form, that malignant LNs have a larger short axis when compared to benign LN in a retrospective cohort of nonlung cancer patients, similar to our cohort.

Our findings confirmed that previously described classic features of neoplastic involvement of a LN, that include sharp borders and larger dimensions, especially the short axis, are also predictors of a LN malignancy in our distinct cohort of patients. Our study population differs from prior reported cohorts as it consisted of patients with ML without known lung cancer. As the combined use of EBUS and EUS becomes progressively more accepted for the staging of pulmonary tumors, studies with

**Table 5: Predictive characteristics for malignancy by number of classic echofeatures**

Number of echofeatures	Malignant LN N (%)	Benign LN N (%)	OR	P value	Sensitivity (%)	Specificity (%)	Correctly classified (%)
0	1 (6)	16 (94)	1.00	-	100	0.0	22.6
1	6 (14)	38 (86)	2.52	0.408	95.2	22.2	38.7
2	3 (20)	12 (80)	4.00	0.254	66.7	75.0	73.1
3	8 (62)	5 (38)	25.6	0.006	52.4	91.7	82.8
4	3 (75)	1 (25)	48.00	0.012	14.3	98.6	79.6

populations without lung cancer will gain importance in the evaluation of the accuracy of EUS and EUS-FNA. The number of classical LN echofeatures in our cohort was also associated with malignant involvement of LN, similar to prior series.<sup>[4,5]</sup>

Although superiority of EUS-FNA over echofeatures has been well documented,<sup>[4,5]</sup> it is possible that the combination of those features and new technique such as EUS-elastography<sup>[18]</sup> will improve the accuracy of EUS in selecting LNs to be sampled.

Limitations of our study included retrospective analysis of data. Moreover, the majority of LNs of our cohort were located at level 7, which may be explained by referral bias regarding the utility of EUS-FNA in this subset of patients. The other limitation is the lack of surgery in all patients. We used a compound reference standard similar to other investigations in the field.

In conclusion, in patients referred to EUS-guided FNA for ML without known lung cancer, increased risk of malignancy was associated with history of prior cancer, larger dimensions of the short axis and presence of sharp borders. The combination of the above predictors might help endoscopists perform FNA in LNs that are more likely malignant, thus minimizing unnecessary biopsies and an increase in overall efficiency of EUS-guided FNA for ML.

#### Capsule summary

In a retrospective cohort of 108 patients without known lung cancer who underwent EUS-guided FNA for ML at a tertiary center, the risk of LN malignancy was associated with prior history of cancer, larger short LN axis, and presence of LN EUS sharp borders.

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