# The role of endobronchial ultrasound elastography in the diagnosis of mediastinal lymph nodes

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***Background*** Endobronchial ultrasound (EBUS) has become a powerful tool for the diagnosis of mediastinal and hilar lymph nodes (LNs). Elastography has been introduced recently to provide more accurate data about the lesions seen during EBUS.

***Aim*** The aim of this study was to evaluate the role of elastography during EBUS for the diagnosis of hilar and mediastinal LN.

***Patients and methods*** We carried out a prospective, cross-sectional study. Patients with hilar/mediastinal LN enlargement on computed tomography examination were included. Convex probe EBUS was performed using conventional B-mode and elastography with transbronchial needle aspiration from the examined LN. All data are presented as mean±SD. Receiver operating characteristic analysis was carried out to find the relative sensitivity and specificity of EBUS elastography and to compare the results with other B-mode findings such as mediastinal LNs.

***Results*** A total of 147 LNs from 56 patients were examined. Malignancy was found in 111 of them. The strain ratio was found to be more accurate when compared with other findings of B-mode when comparing malignant and benign LNs with a cut-off value of 7.5, giving a sensitivity of 95.5% and a specificity of 91.67%. About 63% of malignant LNs were diagnosed from the first pass with the help of elastography.

***Conclusion*** Elastography is a very helpful tool for diagnosing mediastinal LNs with a strain ratio above 7.5, having a strong suggestion of malignancy. Elastography can help in directing the needle during EBUS-transbronchial needle aspiration to reach the final diagnosis with the least possible number of passes and avoiding unnecessary punctures (ClinicalTrials.gov Identifier: NCT02724059).

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## Introduction

Staging of lung cancer determines its treatment and prognosis. Different procedures are used to evaluate mediastinal lymph nodes (LNs) [1]. Non-small-cell lung cancer guidelines recommend endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) of mediastinal LNs as a first-choice method [2].

It is routinely performed on a day-care basis, and provides adequate samples for cytology, histology, and molecular and microbiological diagnostics [3].

Ultrasonic images are used to predict mediastinal LN metastasis [4]. However, round, heterogeneous echoes and edge clarity are independent predictors for assessing malignant LNs [5].

Elastography is an imaging procedure that can assess the biomechanical characteristics of tissues and their deformation under compression [6]. Malignancy can cause formation of stiffer tissue. Elastography can measure tissue stiffness during EBUS-TBNA, exhibiting potential application to the noninvasive discrimination between benign and malignant nodes [5].

The aim of the present study was to evaluate the role of elastography during EBUS-TBNA in the diagnosis of mediastinal/hilar LNs detected by thoracic computed tomography (CT).

## Patients and methods

### Patients

This prospective study was conducted between November 2015 and October 2016 in the endoscopy unit of Tanta University International Educational Hospital. A total of 56 patients were recruited for this study. All patients with hilar/mediastinal LN enlargement on thoracic CT scan, whether there was known lung malignancy (for staging purpose) or not (for diagnosing purpose), were included. Any enlarged LN visible in the chest CT was included. Patients with cardiovascular instability, bleeding diathesis (international normalized ratio >1.3 or platelet count of $<50\ 000/mm^3$), borderline respiratory failure, or lack of cooperation were excluded. There was no randomization, because all subjects meeting inclusion criteria during the study period in our hospital were included. Sample size was calculated to obtain the highest power of the study.

Written informed consent was obtained from all patients included in this study, and the study protocol was approved by the ethics committee of Faculty of Medicine, Tanta University and was registered in clinicaltrial.gov under the number NCT02724059.

#### Convex probe EBUS-guided TBNA and elastography procedure

Bronchoscopy using Pentax EPK-i5000; Pentax, Tokyo, Japan, was performed under moderate sedation under topical anesthesia (2% xylocaine) and under moderate sedation (3–12 mg intravenous midazolam in incremental doses with average of 7.56±1.83 mg) through the oral route in the supine position within 5 days after CT examination.

Real-time EBUS B-mode and elastography with measurement of strain ratio were performed using HI VISION Avius; Hitachi Company, Tokyo, Japan. Color Doppler ultrasound was used to avoid puncture of surrounding vascular lesions.

LNs were identified according to Mountain's regional LN classification system [7]. The target LNs were examined by conventional B-mode ultrasound to assess the shape, echogenicity, edge definition, and diameter.

The elastography mode was used for all targeted LNs. By setting the equipment to the required mode, the scan range included the entire LN and the surrounding normal tissue to assess the elasticity of the targeted LN in comparison with the normal surrounding tissue. Observations were translated into a color signal that was overlaid on the B-mode image. The colors associated with hard, intermediate, and soft tissues were blue, green, and yellow/red, respectively. The strain ratio was only measured when there was good contact of the transducer. The ultrasound processor measured the strain of the targeted area in the candidate LN 'region of interest (ROI)' while comparing with the normal surrounding tissue of a similar size as a quantitative figure. The strain ratio was measured twice for each targeted LN, and the mean value was calculated. Elastography and calculation of the strain ratio were performed within 2–3 min.

After elastography, a transbronchial biopsy using a 22-G needle (ECHO-HD, 22-EBUS P, Echotip, Ultra; Cook Ireland Ltd, Limerick, Ireland) was performed. The number of passes per patient was recorded. N3 nodes were sampled first and then N2 nodes to avoid contamination in lung cancer patients. Cytological specimens were collected and sent to the laboratory for subsequent analysis by a pathologist who was blinded to the EBUS B-mode features and the elastography values. All patients tolerated the procedure with no recorded complications.

A definitive diagnosis of malignancy from the EBUS-TBNA specimens was considered a positive result. In addition, a diagnosis of tuberculosis or sarcoidosis was made on the basis of the presence of caseating or noncaseating granuloma, respectively, apart from clinical and radiological findings. For negative results or insufficient specimens, 'no adequate number of lymphocytes on the smear', the maneuver was repeated; if the result was still negative, clinical and radiologic follow-up on the LNs for at least 3 months were carried out.

#### Statistical analysis

All data are presented as mean±SD. The receiver operating characteristic curve was analyzed to find the relative sensitivity and specificity of EBUS elastography to compare it with other B-mode mediastinal LNs. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy rate were calculated from the standard definitions used for malignancy diagnosis. All statistical analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, Illinois, USA). Differences were considered statistically significant when $P$ value of less than 0.05.

## Results

The present study included 56 (32 males and 24 females with mean±SD age 52±11.2 years) patients. Elastography and EBUS-TBNA were performed on 147 hilar and mediastinal LN at different stations distributed as follows: 16 located in upper paratracheal stations 2R and 2L, 34 located in lower paratracheal stations 4R and 4L, 51 located in subcarinal station 7, 31 located in hilar group stations 10R and 10L, and 15 located in interlobar group stations 11s, 11i, and 11L. We had 99 LNs with diameters more than or equal to 10 mm at their narrowest region (67.3%), and 48 LN with size of less than 10 mm (32.7%) (Table 1 and Figs 1 and 2).

The cytological examination revealed malignancy in 111 LNs (39 malignant lymphoma and 72 metastatic infiltration) and benign condition in 36 LNs (10 tuberculosis, 11 sarcoidosis, three nonspecific infections such as pneumonia or lung abscess, two infectious mononeucleosis, six reactive LN hyperplasia, and four autoimmune disease). Malignancy was the final diagnosis in 41 patients, and non-neoplastic conditions were found in 15 patients (Fig. 3).

When using elastography, the strain ratio of malignant LNs was 29.9±15.5 significantly higher compared with benign LNs, which was 3.27±2.95 ($t$=17.12 and $P$<0.001). Receiver operating characteristic curve analysis was performed to determine a cut-off value for the strain ratio to differentiate benign from malignant LNs. The cut-off value of the strain ratio was found to be 7.5, above which malignancy should be diagnosed with a sensitivity of 95.5%, a specificity of 91.67%, and an area under the curve of 0.98 (Fig. 4).

**Table 1 Patients' demographics and characteristics**

| | *n* (%) |
|---|---|
| Age (years) | 52±11.2 |
| Sex | |
| Males | 32 (57.14) |
| Females | 24 (42.86) |
| LN stations | |
| 2R and 2L | 16 (10.9) |
| 4R and 4L | 34 (23.1) |
| 7 | 51 (34.7) |
| 10R and 10L | 31 (21.1) |
| 11s, 11i and 11L | 15 (10.2) |
| Size of LN (mean±SD) (mm) | 19.3±8.8 |
| ≥10 | 99 (92 malignant and 7 benign) |
| <10 | 48 (29 benign and 19 malignant) |

LN, lymph node.

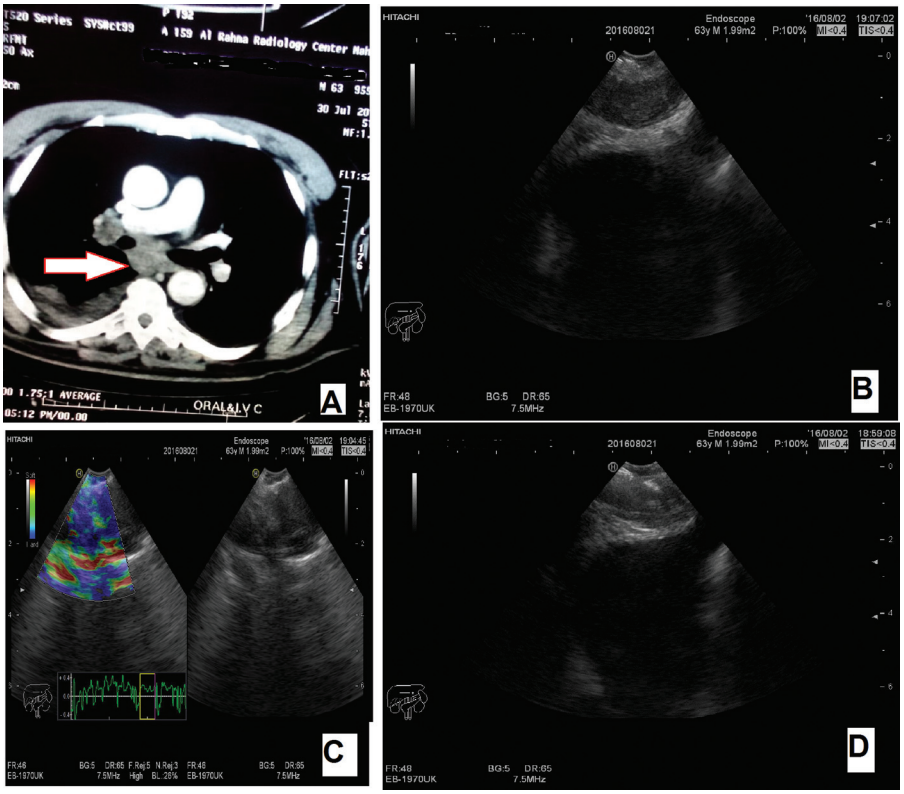
The strain ratio was found to be more accurate when compared with other findings of B-mode during endoscopic ultrasound examination of mediastinal and hilar LNs (Table 2).

The number of passes required for diagnosis in malignant LNs was 1.55±0.783 per LN, which was significantly lower than those in benign LNs, 2.28±1.19 per LN ($t$=3.45 and $P$=0.0012). In the malignant LN group, 70 (63.06%) LNs were diagnosed from the first pass, 21 (18.92%) from the second pass, and 20 (18.02%) from the third pass. However, in the benign LN group, 14 (38.89%) LNs were diagnosed from the first pass, five (13.89%) from the second pass, 10 (27.78%) from the third pass, and seven (19.44%) from the fourth pass.

## Discussion

Elastographic images are generated on the basis of the compressive action generated by the pulsation of vessels in the thoracic cavity and respiratory movement.

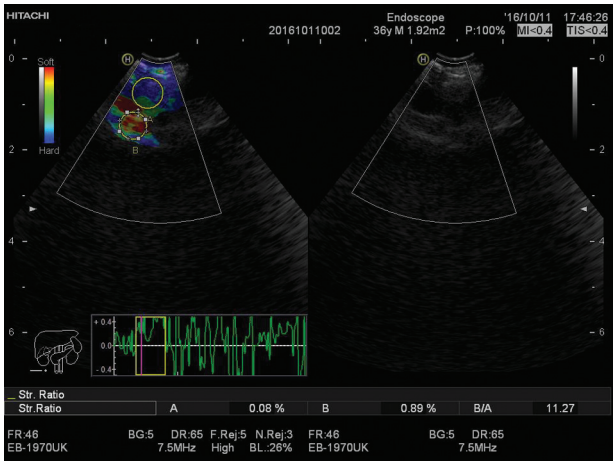
**Figure 1**




A male patient aged 63 years presented with mediastinal lymphadenopathy. (a) Enlarged subcarinal lymph node (station 7) in computed tomography (CT). (b) Endobronchial ultrasound (EBUS) shows hypoechoic lesion with definite margin. (c) Elastography on the targeted lymph node can localize the area of interest [region of interest (ROI)]. There is predominant blue color, giving an impression of malignancy (strain ratio was 27.6). (d) Transbronchial needle aspiration (TBNA) under guidance of EBUS from ROI

The elasticity of tissue within the scanned area is reconstructed by comparing it with the surrounding tissue; observations are translated into a color signal that is overlaid on the B-mode image. The colors associated with hard, intermediate, and soft tissues are blue, green, and yellow/red, respectively [5]. Moreover, it is possible to quantify the strain in two operator-selected areas. Comparing these different areas of tissue allows a numeric representation of the strain ratio between the two areas [8].

**Figure 2**




The elastography strain ratio measured the strain of the region of interest (the upper circle) compared with the normal surrounding tissue (lower circle) of similar size as a quantitative figure (strain ratio is 31.2)

In the present study, 56 (32 males and 24 females) patients were included to examine 147 hilar and mediastinal LN in different stations. Among the 147 LN, 111 of them were malignant (39 malignant lymphoma and 72 metastatic infiltration) and 36 were benign (10 tuberculosis, 11 sarcoidosis, three nonspecific infections such as pneumonia or lung abscess, two infectious mononeucleosis, six reactive LN hyperplasia, and four autoimmune disease). Malignancy was the final diagnosis in 41 patients, and benign conditions were found in 15 patients.

The number of patients and the number of examined LNs in the present study were larger than other studies

**Figure 3**

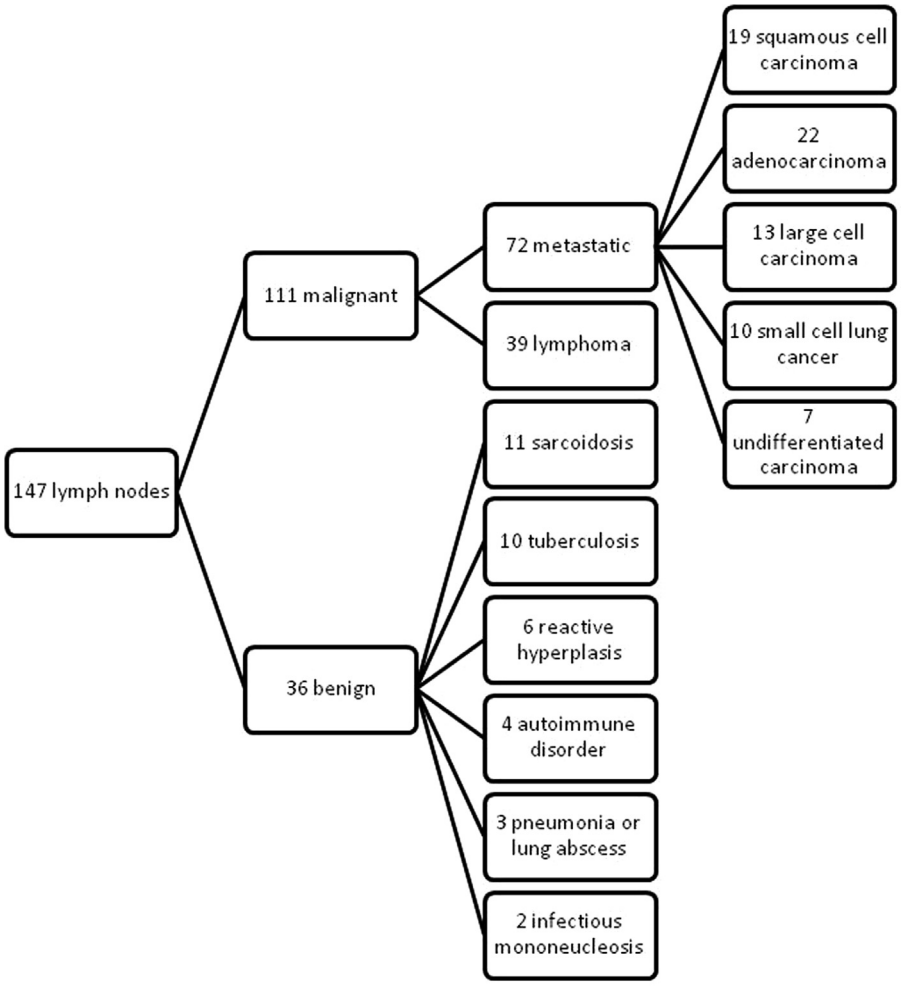



Diagram shows the cytological diagnosis of the examined lymph nodes

[4,9,10]. In the study carried out by He *et al.* [4], 40 (26 males, 14 females) patients underwent elastography, and EBUS-TBNA was performed on 68 hilar and mediastinal LNs, among which 42 were malignant LNs (12 squamous cell carcinomas, 11 adenocarcinomas, nine small-cell lung cancers, and 10 low-differentiation cancer). Only 26 LNs were benign.

In another study by Izumo *et al.* [10], there were 30 (17 males, 13 females) patients who underwent elastography with EBUS-TBNA. 75 hilar and mediastinal LNs were sampled. Histological examination of the EBUS-TBNA specimens revealed 42 malignant LNs and 33 benign LNs.

In our study, among the examined 147 LNs, there were 16 in stations 2R and 2L, 34 in stations 4R and 4L, 51 in subcarinal station 7, 31 in stations 10R and 10L, and 15 in stations 11s, 11i, and 11L. These findings are comparable with that of He *et al.* [4], who found that among the observed 68 LNs 12 were located in group 2R, 15 in groups 4R and 4L, 21 in group 7, 11 in groups 10R and 10L, and nine in groups 11s, 11i, and 11L.

In the present study, the strain ratio of malignant LNs was 29.9±15.5 significantly higher than that of benign LNs, which was 3.27±2.95. The cut-off value of the strain ratio to differentiate benign from malignant LNs was found to be 7.5, above which malignancy can be diagnosed with a sensitivity of 95.5%, a specificity of 91.67%, and an area under the curve of 0.98.

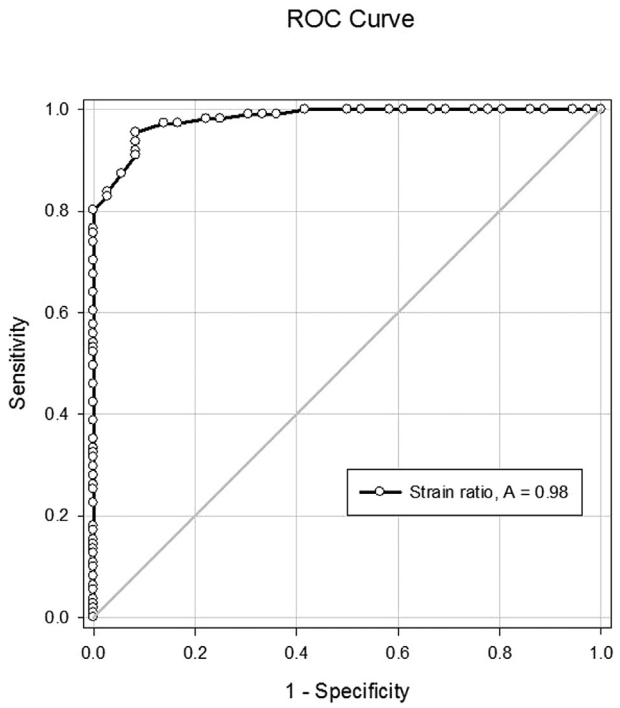
Rozman *et al.* [8] found similar results as the strain ratio for malignant nodes was 18.96±18.32 and 6.27±7.30 for benign nodes. The area under the curve was 0.87 at an optimal cut-off point for strain ratio of 8 to distinguish malignant and benign LNs with an accuracy of 86.25% (sensitivity 88.24%, specificity 84.78%, positive predictive value 81.08%, and negative predictive value 90.70%).

On the other hand, in the study by He *et al.* [4], the strain ratio of malignant LNs was significantly higher than that of their benign counterparts (87.69±49.15 vs. 20.60±17.14), and the cut-off value was 32.07. The differences in the values between that study and ours may be due to the difference in study population number and the nature of the underlying cause.

In our study, the strain ratio was found to be more accurate when compared with other findings of B-mode (such as size, border, echogenecity, and uneven distribution of echogenecity) in differentiating malignant and benign conditions. This finding was consistent with what was found in other studies [4,10], and this shows the importance of elastography while performing EBUS/TBNA.

Another beneficial aspect of our study is that elastography enabled us to reduce the number of passes required for diagnosing the nature of LNs, especially for the malignant lesions. The number of passes required for diagnosis in malignant LNs was significantly lower than those in

**Figure 4**




ROC curve for strain ratio to differentiate malignant and benign lymph nodes

**Table 2 Comparison between strain ratio and other B-mode findings for differentiating malignant from benign lymph nodes**

| | Strain ratio ≥7.5 | LN size in short diameter ≥1 cm | Distinct border | Hypoechoeic LN | Uneven echogenecity |
|---|---|---|---|---|---|
| Sensitivity | 95.5 | 82.88 | 72.97 | 62.16 | 53.15 |
| Specificity | 91.67 | 80.56 | 63.89 | 55.56 | 61.11 |
| PPV | 97.25 | 92.93 | 86.17 | 81.18 | 80.82 |
| NPV | 86.84 | 60.42 | 43.4 | 32.26 | 29.73 |
| Accuracy | 94.56 | 82.31 | 70.75 | 60.54 | 55.1 |
| AUC | 0.98 | 0.87 | 0.81 | 0.74 | 0.70 |

AUC, area under the curve; LN, lymph node; NPV, negative predictive value; PPV, positive predictive value.

benign LNs. In the malignant LN group, 70 (63.06%) LNs were diagnosed from the first pass, whereas in the benign LN group 14 (38.89%) LNs were diagnosed from the first pass. With the use of elastography, we were able to direct the needle to the area inside LN, which can give the best yield during histopathological examination to avoid unnecessary punctures.

The present study was the first to be carried out in our country and in Africa, which used elastography for the diagnosis of enlarged hilar or mediastinal LNs. It also adds to the existing data about elastography and helps find an accurate cut-off value of strain ratio to differentiate between malignant and benign mediastinal LNs.

One limitation of our study was the relative small number of patients included, which may have affected the accuracy of the cut-off value. However, this is because it was a single-center experience. In addition, the number of patients and LNs in our study was greater than the number included in other studies. Multicenter studies or meta-analyses are needed to obtain better results and more accurate outcome.

## Conclusion

Elastography is a very helpful tool for diagnosing mediastinal LNs with a strain ratio above 7.5 having a strong suggestion of malignancy. Elastography can help in directing the needle during EBUS-TBNA to reach the final diagnosis with the least possible number of passes to avoid unnecessary punctures.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

## References

1 McPhail S, Johnson S, Greenberg D, Peake M, Rous B. Stage at diagnosis and early mortality from cancer in England. *Br J Cancer* 2015; **112**: S108–S115.

2 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** (Suppl):e211S–e250S.

3 Vaidya PJ, Kate AH, Yasufuku K, Chhajed PN. Endobronchial ultrasound-guided transbronchial needle aspiration in lung cancer diagnosis and staging. *Expert Rev Respir Med* 2015; **9**:45–53.

4 He HY, Huang M, Zhu J, Ma H, Lyu XD. Endobronchial ultrasound elastography for diagnosing mediastinal and hilar lymph nodes. *Chin Med J* 2015; **128**:2720–2725.

5 Fujiwara T, Yasufuku K, Nakajima T, Chiyo M, Yoshida S, Suzuki M, *et al.* The utility of sonographic features during endobronchial ultrasound-guided transbronchial needle aspiration for lymph node staging in patients with lung cancer: a standard endobronchial ultrasound image classification system. *Chest* 2010; **138**:641–647.

6 Saftoiu A, Vilman P. Endoscopic ultrasound elastography – a new imaging technique for the visualization of tissue elasticity distribution. *J Gastrointestin Liver Dis* 2006; **15**:161–165.

7 Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997; **111**:1718–1723.

8 Rozman A, Malovrh MM, Adamic K, Subic T, Kovac V, Flezar M. Endobronchial ultrasound elastography strain ratio for mediastinal lymph node diagnosis. *Radiol Oncol* 2015; **49**:334–340.

9 Nakajima T, Yasufuku K, Saegusa F, Fujiwara T, Sakairi Y, Hiroshima K, *et al.* Rapid on-site cytologic evaluation during endobronchial ultrasound-guided transbronchial needle aspiration for nodal staging in patients with lung cancer. *Ann Thorac Surg* 2013; **95**:1695–1699.

10 Izumo T, Sasada S, Chavez C, Matsumoto Y, Tsuchida T. Endobronchial ultrasound elastography in the diagnosis of mediastinal and hilar lymph nodes. *Jpn J Clin Oncol* 2014; **44**:956–962.