

## ORIGINAL ARTICLE

# Diagnostic value of endobronchial ultrasound elastography for the differentiation of benign and malignant intrathoracic lymph nodes

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## ABSTRACT

**Background and objective:** Endobronchial ultrasound (EBUS) findings can be used for benign/malignant differentiation of lymph nodes (LN). Recently, EBUS elastography has been introduced as a complementary modality in the evaluation of intrathoracic lymphadenopathy. We evaluated the ability of EBUS elastography to differentiate between benign and malignant LN.

**Methods:** A prospective study was conducted on patients sent for evaluation of intrathoracic lymphadenopathy. LN were classified qualitatively according to elastographic colour pattern: type 1, predominantly non-blue; type 2, partly blue, partly non-blue and type 3, predominantly blue. Quantitative elastography of LN was measured by the strain ratio (SR). Qualitative and quantitative elastographies were compared for the final diagnosis of LN.

**Results:** There were 120 LN from 72 patients who underwent EBUS elastography. The final diagnosis included 96 malignant and 24 benign LN. All of the 16 type 1 LN proved to be benign diseases, while 95 of the 101 type 3 LN were finally diagnosed as malignancies. Three LN classified as type 2 proved to be two benign and one malignant. Malignant LN presented a higher median SR than benign LN (73.50 vs 1.29,  $P = 0.001$ ). An SR of >2.5 and non-type 1 elastographic pattern achieved similar diagnostic performance in benign/malignant differentiation (sensitivity, 100% vs 100%; specificity, 70.8% vs 66.7%; positive predictive value, 93.2% vs 92.3%; negative predictive value, 100% vs 100%).

**Conclusion:** EBUS elastography is a promising diagnostic modality for the differentiation of benign and malignant LN during EBUS-guided transbronchial needle aspiration (TBNA). Qualitative and quantitative EBUS elastographies provide similar diagnostic performance.

**Key words:** elastography, endobronchial ultrasound, endobronchial ultrasound-guided transbronchial needle aspiration, malignancy, strain ratio.

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## SUMMARY AT A GLANCE

Endobronchial ultrasound elastography has been introduced as a complementary modality in benign/malignant differentiation of intrathoracic lymphadenopathy. We found that a strain ratio of >2.5 and non-type 1 elastographic pattern achieved similar high diagnostic performance in benign/malignant differentiation. It can be useful for targeting a suspicious lymph node for sampling.

**Abbreviations:** AUC, area under the ROC curve; CP, convex probe; CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS, endoscopic ultrasound; LN, lymph node; NPV, negative predictive value; NSCLC, non-small cell lung cancer; PPV, positive predictive value; RGB, red, green and blue; ROC, receiver operating characteristic; ROI, region of interest; SR, strain ratio; TB, tuberculosis; TBLB, transbronchial lung biopsy; TTNA, transthoracic needle aspiration; VATS, video-assisted thoracoscopic surgery.

## INTRODUCTION

First introduced in 2002,<sup>1</sup> endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is now widely used by interventional pulmonologists for sampling intrathoracic lymph nodes (LN). With real-time ultrasound guidance, it improves accuracy and safety of LN aspiration. In recent studies, EBUS-TBNA has been shown to have a superior diagnostic yield than conventional TBNA, and has a diagnostic accuracy comparable to mediastinoscopy in intrathoracic LN evaluation.<sup>2–4</sup> However, during the procedure physicians usually encounter various LN detected by EBUS. Prediction of the nature of pathological LN before puncture may help physicians select suspicious LN to obtain tissue for diagnosis without excessive passes.

Sonographic features are useful for the differentiation of benign and malignant intrathoracic LN.<sup>5,6</sup> Adding power/colour Doppler-mode image analysis to EBUS B-mode to examine the vascular patterns of LN helps improve the accuracy of differentiation.<sup>6,7</sup> Although some sonographic and vascular patterns are present in malignant rather than benign LN, a combination of

these findings are needed to help precise differentiation between the two. Wang *et al.*<sup>6</sup> reported that at least two of the four sonographic and vascular patterns (round shape, presence of matting, absence of central hilar structure and non-hilar vascular pattern perfusion) could achieve the best diagnostic performance for predicting metastatic LNs with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of 93.03%, 55.68%, 84.55%, 75.38% and 82.68%, respectively.

Ultrasound elastography is a new imaging method used for measurement of tissue elasticity. The method reveals the physical properties of the tissue by characterizing the difference of hardness between pathological tissue and normal tissue in response to compression or vibration.<sup>8,9</sup> Data can then be converted into an RGB (red, green and blue) colour image where hard tissue is shown in blue, medium tissue in green and soft tissue in red, overlaid on the B-mode image. On the basis of pathophysiology that malignancy causes tissue to be harder than adjacent normal tissue, ultrasound elastography can be used for benign/malignant differentiation in several organs such as breast, thyroid, prostate, cervix, liver, pancreas and extrathoracic LNs.<sup>10</sup> Recently, EBUS elastography has been introduced as a complementary modality in the evaluation of intrathoracic lymphadenopathy. At present, data regarding the use of EBUS elastography for the differentiation of benign and malignant intrathoracic LNs remain limited. The aim of this study was to evaluate the ability of elastography to differentiate between benign and malignant LNs in patients undergoing EBUS for investigation of enlarged intrathoracic LNs. In addition, both qualitative and quantitative EBUS elastography were compared.

## METHODS

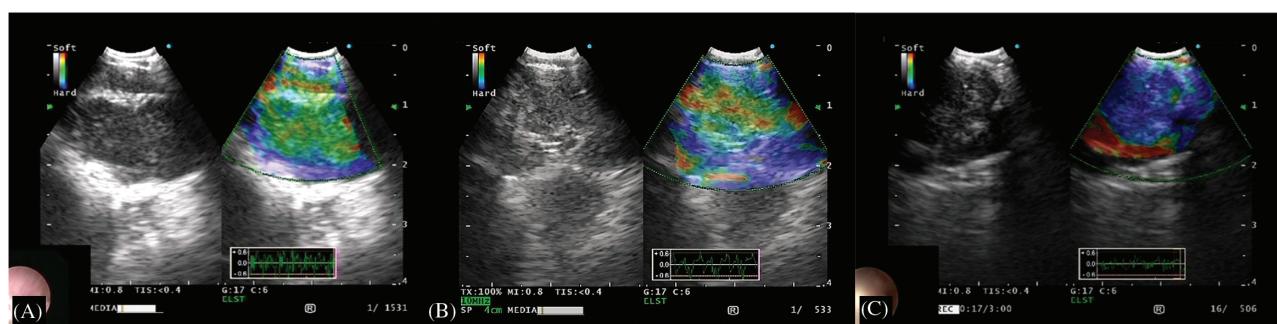
A prospective study was conducted at Ramathibodi Hospital, Mahidol University, and Rajavithi Hospital, Rangsit University, Thailand from July 2015 to July 2016 on patients  $\geq 15$  years of age who were sent for evaluation of enlarged intrathoracic LNs demonstrated on computed tomography (CT) scan of the chest. Only accessible LNs identified by EBUS-TBNA were

included. Short axis diameter of the target node was recorded. Written informed consent was obtained from all patients before commencement of the EBUS-TBNA procedure. The study protocol was approved by the Ethical Review Committee, Institutional Review Board of Rajavithi Hospital (ID 084-2558) and the Ethics Committee on Human Experimentation of Ramathibodi Hospital, Faculty of Medicine, Mahidol University (ID 06-58-16).

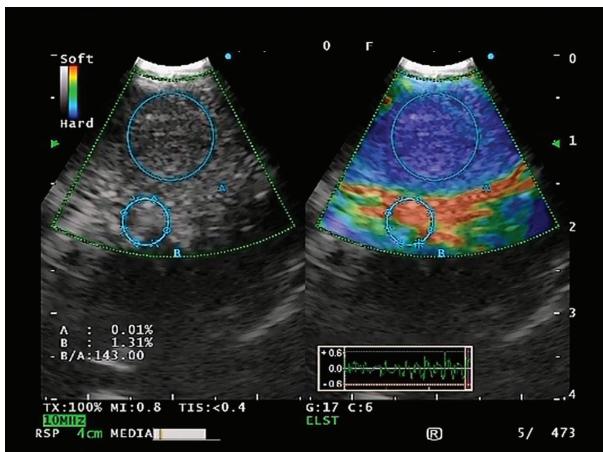
All EBUS procedures were performed via the oral route under local anaesthesia (lidocaine) and conscious sedation (pethidine) by P.K. or V.B. EBUS was performed using a real-time convex probe EBUS (BF-UC180F; Olympus, Tokyo, Japan) linked to a processor (EU-ME2 Premier Plus; Olympus) with a frequency of 10 MHz. The target LNs detected by CT scan were initially identified by conventional B-mode EBUS and then elastography was performed. LNs were classified qualitatively according to the dominant elastographic colour pattern: type 1, predominantly non-blue; type 2, partly blue, partly non-blue and type 3, predominantly blue (Fig. 1).<sup>11</sup> In cases where multiple LNs were detected, bizarre, large and easy-to-sample LNs were selected for further examination. To assess interobserver agreement in qualitative colour elastography, still images of all selected LNs undergoing elastography were captured and reviewed independently by the operator not present at the initial procedure (P.K. or V.B.).

Quantitative elastography of selected LNs was performed by measurement of the strain ratio (SR). The largest possible area within the LN was outlined (circle) as A, while the area of the surrounding tissue was outlined as B, as a reference. The strain (B/A) ratio was calculated automatically by the ultrasound unit (Fig. 2).<sup>12</sup> The SR for each LN was measured three times and the median value used for analysis. Then, EBUS-TBNA was performed with a dedicated 22-gauge cytology TBNA (NA-201SX-4022; Olympus) on selected LNs. Samples from each LN were submitted for cytopathology and analysed separately.

The diagnosis from EBUS-TBNA was established as the cytopathological report. The cytopathological diagnosis of nonspecific lymphadenopathy was considered to be nondiagnostic even if the final diagnosis proved to be a benign process. If the definite diagnosis was not



**Figure 1** Qualitative endobronchial ultrasound (EBUS) elastography classification of lymph nodes according to the dominant elastographic colour pattern: (A) type 1, predominantly non-blue; (B) type 2, partly blue, partly non-blue and (C) type 3, predominantly blue. Cytopathological results from EBUS-guided transbronchial needle aspiration (TBNA) were tuberculosis, adenocarcinoma, and adenocarcinoma, respectively.



**Figure 2** Strain ratio measurement in type 3 endobronchial ultrasound (EBUS) elastography colour pattern subcarinal lymph node (LN). The largest possible area within the LN was outlined as A. An area of the normal-appearing soft tissue outside the LN was selected as B. The strain (B/A) ratio was 143.00. The final diagnosis obtained by EBUS-guided transbronchial needle aspiration (TBNA) was adenocarcinoma.

reached by EBUS-TBNA, the patient then underwent video-assisted thoracoscopy or clinical and radiological follow-up to confirm the underlying cause of the lymphadenopathy.

### Statistical analysis

All data were analysed using the SPSS statistical software package, version 16.0 for Windows (SPSS, Chicago, IL, USA). Data for continuous variables were expressed as mean  $\pm$  SD, and those of categorical variables were presented as percentage. The kappa statistic was used to test for interobserver variability in qualitative EBUS elastography interpretation.

Nonparametric Mann-Whitney U-test was used to compare the SR between benign and malignant LNs. A receiver operating characteristic (ROC) curve was constructed and the area under the ROC curve (AUC) with 95% CI was determined to find the cut-off SR for differentiating between benign and malignant LNs.

The sensitivity, specificity, PPV, NPV and AUC of both qualitative and quantitative elastographies were compared with the final diagnosis of LNs. All statistical tests were two-sided and  $P < 0.05$  was considered statistically significant.

## RESULTS

Seventy-two patients, comprising 41 males and 31 females with a mean age of  $58.3 \pm 12.5$  years, underwent EBUS elastography, with a total of 120 LNs studied. The mean LN size was  $18.8 \pm 7.9$  mm, 96 were malignant and 24 benign. The baseline characteristics of the patients and target LNs are given in Table S1 (Supplementary Information).

Cytopathology of EBUS-TBNA samples provided a definite diagnosis in 103 LNs (85.8%). For 17 patients whose EBUS-TBNA cytopathological results were

non-diagnostic, the final diagnoses were 5 malignant and 12 benign causes of the lymphadenopathy. One malignancy was definitively diagnosed by video-assisted thoracoscopic surgery (VATS). Non-small cell lung cancer (NSCLC) was diagnosed by transbronchial lung biopsy (TBLB) in three patients and by transthoracic needle aspiration (TTNA) in one patient. Regarding benign final diagnoses, five patients were diagnosed as tuberculosis (TB): established by VATS in two patients, positive TB culture from EBUS-TBNA rinse fluid in one and demonstrating caseous granuloma from TBLB samples and LN regression after administration of anti-tuberculous drugs in two patients. Seven LNs were stable in size on follow-up CT scan at 6 months and were finally concluded to be reactive LNs (Fig. S1, Supplementary Information).

In qualitative EBUS elastography interpretation, the kappa value to assess the interobserver variability was 0.88. There were no cases of disagreement in interpretation from type 1 to type 3 and vice versa. Table 1 shows the distribution of LNs according to qualitative EBUS elastography type and final diagnosis. All type 1 LNs were diagnosed as benign, while 94.1% of type 3 were malignant.

Malignant LNs presented a higher median SR than benign LNs (73.50 (range: 2.93–305.00) vs 1.29 (range: 0.03–194.00),  $P < 0.001$ ). The AUC for the SR was 0.85 (95% CI: 0.74–0.97; Fig. S2, Supplementary Information). Using an ROC curve, the best cut-off SR for differentiation of benign and malignant LNs was 15.3. The cut-off SR of  $>2.5$  provided sensitivity of 100% for predicting malignant LN. In comparing qualitative and quantitative EBUS elastography, non-type 1 elastographic pattern and SR of more than 2.5 and 15.3, respectively, achieved similar diagnostic performance in benign/malignant differentiation ( $P = 0.77$ ) (Table 2).

**Table 1** Qualitative EBUS elastography classification of LNs according to the dominant elastographic colour pattern and final diagnosis

Elastography type	Benign LNs, n (%)	Malignant LNs, n (%)
Type 1 (n = 16)	16 (100)	0 (0)
Type 2 (n = 3)	2 (66.7)	1 (33.3)
Type 3 (n = 101)	6 (5.9)	95 (94.1)

EBUS, endobronchial ultrasound; LN, lymph node.

**Table 2** Comparison of diagnostic performance for qualitative and quantitative EBUS elastographies in benign/malignant differentiation

	Sensitivity	Specificity	PPV	NPV	AUC
Non-type 1	100.0	66.7	92.3	100.0	0.83
SR > 2.5	100.0	70.8	93.2	100.0	0.85
SR > 15.3	87.5	79.2	94.4	61.3	0.83

AUC, area under the receiver operating characteristic curve; EBUS, endobronchial ultrasound; NPV, negative predictive value; PPV, positive predictive value; SR, strain ratio.

**Table 3** Diagnostic performance for qualitative and quantitative EBUS elastographies in benign/malignant differentiation according to the LN size

LN size	Aetiology	Elastographic colour pattern		Strain ratio	
		Type 1	Non-type 1	<2.5	>2.5
<10 mm (n = 15)	Benign	3	2	3	2
	Malignancy	0	10	0	10
10–20 mm (n = 58)	Benign	9	4	10	3
	Malignancy	0	45	0	45
≥20 mm (n = 47)	Benign	4	2	4	2
	Malignancy	0	41	0	41
All (n = 120)	Benign	16	8	17	7
	Malignancy	0	96	0	96

EBUS, endobronchial ultrasound; LN, lymph node.

In overall LNs, SR had no correlation with the LN size ( $r = 0.005$ ;  $P = 0.954$ ). Both qualitative and quantitative EBUS elastographies provided good diagnostic performance in benign/malignant differentiation regardless of the size of the LN (Table 3).

## DISCUSSION

Intrathoracic LNs were first evaluated using elastography during endoscopic ultrasound (EUS) via the oesophagus. Janssen *et al.*<sup>13</sup> reported that the diagnostic accuracy range in evaluation of posterior mediastinal LNs was 84.6–86.4% for malignant LNs and 81.8–87.9% for benign LNs. For nodal staging of oesophageal cancer, EUS elastography showed superior accuracy compared with conventional EUS criteria in differentiating benign and malignant LNs.<sup>14</sup>

Ultrasound elastography has been integrated into convex probe EBUS. To our knowledge, only five English-language publications have evaluated its usefulness in intrathoracic LN evaluation (Table 4).<sup>11,15–18</sup> The characteristics of tissue elasticity can be measured either by the colour-based qualitative method or by a quantitative method. For the qualitative method, LNs are classified according to the dominant elastographic colour patterns. Izumo *et al.*<sup>11</sup> demonstrated its accuracy in predicting type 1 (benign) and type 3 (malignant) LNs, but not type 2, similar to our results.

Owing to subjective interpretations, three quantitative techniques have been developed to improve accuracy and minimize operator bias. The first is the strain histogram, which represents the mean strain value within a selected area. In the histogram graph, the x-axis represents the elasticity values (each value indicated by a pixel colour) from 0 to 255, where 0 is hardest and 255 is softest, and the y-axis represents the number of pixels of each value.<sup>19</sup> Unfortunately, data regarding the efficacy of this technique are limited.<sup>15</sup> The second method is the stiff area ratio. The operator must first define the region of interest (ROI) that covers the largest possible area within the LN. Then, the stiff area ratio can be calculated by the blue-coloured (defined as hue 145–180) pixel area divided by the LN pixel area in the

ROI. Nakajima *et al.*<sup>16</sup> demonstrated a cut-off stiff area ratio of 0.311 for predicting malignant LN. However, this method requires additional software and cannot be performed under real-time EBUS procedure. The final technique is the SR, which is based on a comparison between two non-overlapping tissue areas; usually area A is the lesion, area B is the reference zone and the SR represents the B/A quotient.<sup>19</sup> As the present results indicate, the SR has shown efficacy in benign/malignant differentiation in previous studies.<sup>17,18</sup>

To provide a definitive diagnosis of the cause of intrathoracic lymphadenopathy, a tissue diagnosis is usually required; however, multiple LNs are frequently discovered during both CT scan and EBUS investigations. When malignancy is suspected pre-procedure, the most suspicious LN should be targeted for sampling. Benign/malignant differentiation is necessary for accurate LN staging of lung cancer, in this context LNs which are potentially involved in disease should be sampled, while benign-looking LNs might be avoided to reduce unnecessary LN punctures. After sampling, if a malignant tissue is not obtained, then the physician has to interpret whether this represents a true negative. Thus, the test should have high sensitivity and high NPV. Although there was a high sensitivity and NPV of nearly 90% at the cut-off SR used in previous reports, this still cannot preclude LN sampling and confirm a true negative result. Therefore, we chose the cut-off SR of >2.5 to achieve sensitivity and NPV of 100%. Qualitative colour EBUS elastography of non-type 1 LNs also provided similar diagnostic results in prediction of malignancies.

Although qualitative colour elastography is a subjective measurement, we found that interobserver agreement was excellent, with no cases of misinterpretation between type 1 and type 3. Elastography of type 2 LNs may be either benign or malignant; hence, aspiration should be carried out, focusing on the blue region. In contrast, we found that SR, which is a quantitative measurement, had intraobserver variability. Thus, each LN was measured three times and the median value was selected for analysis. The difference in ROI areas in both LN and the surrounding normal tissue has an influence on SR value. Nevertheless, with a low cut-off SR of 2.5, this variability does not result in misinterpretation when differentiating between benign and malignant nodes.

There were some limitations in our study. The indication for EBUS procedure in our study was to obtain an initial diagnosis, not for LN staging of lung cancer. Therefore, the results could be different when applied for LN staging, implying that further work on EBUS elastography for LN staging is still necessary. Second, the mean diameter of LNs in our study was relatively large, with a limited number of LNs that were <10 mm. Results may be different in small nodes that contain malignant deposits, and therefore EBUS elastography findings in early metastasis containing LNs that remain small in size is another issue that requires further investigation. Third, in cases of high likelihood of malignancy, only type 2 and 3 LNs were selected for sampling; hence, we might have missed the possibility of malignancy in type 1 LNs in such cases. Fourth, TB lymphadenitis was the cause of the majority of benign LNs in our study, which is reflective of the prevalence of the disease in our population. Other causes of

**Table 4** Details of previous reports studying EBUS elastography for intrathoracic lymphadenopathy (Pentax, Tokyo, Japan) (Olympus, Tokyo, Japan)

Author (year(s) when study was conducted)	Patients (n), LN (n), Malignant LN (n, %)	Comparator	CP-EBUS	Measurement	Outcome
Trosini-Désert <i>et al.</i> <sup>15</sup> (2012)	10 13 5 (38.5)	Cytopathology from EBUS-TBNA	EB-1970, Pentax	Quantitative histogram analysis	Malignant LNs had lower mean histogram and higher hard areas than benign LNs
Izumo <i>et al.</i> <sup>11</sup> (2014)	30 75 42 (56.0)	Cytopathology from EBUS-TBNA	BF-UC260FW, Olympus	Qualitative colour elastography: type 1, predominantly non- blue; type 2, partly blue, partly non-blue; type 3, predominantly blue	Classifying type 1 as benign and type 3 as malignant, the sensitivity, specificity, PPV, NPV and diagnostic accuracy rates were 100%, 92.3%, 94.6%, 100% and 96.7%, respectively
Nakajima <i>et al.</i> <sup>16</sup> (2013)	21 49 16 (32.6)	Cytopathology from EBUS-TBNA	BF-UC260FW, Olympus	Quantitative stiff area ratio calculated by area (pixel) of blue colour (hue 145–180) divided by the entire target LN area	Using a cut-off value of 0.311 for the stiff area ratio, the sensitivity and specificity for predicting metastatic disease were 0.81 and 0.85, respectively
He <i>et al.</i> <sup>17</sup> (2014–2015)	40 68 42 (61.8)	Cytopathology from EBUS-TBNA and surgery in negative EBUS- TBNA cases	EB-1970, Pentax	Qualitative colour elastography: 1 point, non-blue > 80%; 2 points, non-blue 50–80%; 3 points, blue 50–80%; 4 points, blue > 80%	The elastography grading score was higher for malignant LNs than benign LNs ( $3.35 \pm 0.91$ vs $1.84 \pm 0.97$ , $P < 0.001$ )
Rozman <i>et al.</i> <sup>18</sup> (2013)	33 80 34 (42.5)	Cytopathology from EBUS-TBNA and surgery or follow- up in negative EBUS-TBNA cases	BF-UC180F, Olympus	Quantitative SR	Using a cut-off value of 32.07 for the SR, the sensitivity, specificity, PPV and NPV were 88.1%, 80.8%, 88.1%, and 85.3% respectively
This study (2015–2016)	72 120 96 (80.0)	Cytopathology from EBUS-TBNA and surgery or follow- up in negative EBUS-TBNA cases	BF-UC180F, Olympus	Quantitative SR	See text

CP, convex probe; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; LN, lymph node; NPV, negative predictive value; PPV, positive predictive value; SR, strain ratio.

benign lymphadenopathy, such as sarcoidosis, should be examined by EBUS elastography colour pattern and SR to confirm our findings. Finally, we did not compare the efficacy of EBUS elastography with B-mode sonographic patterns. B-mode EBUS was also performed in all patients before elastography, but we found that the interpretation was difficult, involving subjective judgment, and might be operator-dependent, while both colour and SR elastography were easier. Although the number of patients was limited, in studies by He *et al.*<sup>17</sup> and Rozman *et al.*<sup>18</sup> SR elastography showed

superior accuracy than B-mode EBUS in differentiating benign and malignant LNs.

In conclusion, EBUS elastography is a promising diagnostic modality for the differentiation of benign and malignant LNs during EBUS-TBNA. Qualitative and quantitative EBUS SR elastographies provide similar diagnostic performance. This technology can be useful for targeting a suspicious LN for EBUS-TBNA sampling. However, more research is needed regarding other aspects, such as indication (diagnosis or staging), LN size (early metastasis), elastography findings in

different types of malignancy and comparison of different elastography techniques (colour, strain histogram, stiff area ratio and SR). In addition, standardization of ROI selection needs to be specified to reduce intraobserver and interobserver variability.

## Disclosure Statement

Preliminary data were previously presented at the ERS International Congress 2016.

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## Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

**Figure S1** Flow diagram of diagnostic work-up in 120 intrathoracic lymph nodes.

**Figure S2** Receiver operating characteristic curve for elastography strain ratio in benign/malignant differentiation.

**Table S1** Baseline characteristics of the study population.