Endobronchial Ultrasound Elastography in the Evaluation of Mediastinal and Hilar Lymph Nodes

Maqsumi Reza[1], Ved Prakash[2], Nivedita[3], Huma Firdaus[4], Syed Ahmad Hussain Kazmi[5], Vikram Gautam[6]

ABSTRACT

Introduction: Endobronchial ultrasound (EBUS) elastography is an imaging procedure for describing the elasticity of intrathoracic lesions and provides important additional diagnostic information. Objective: The purpose of this study was to compare the elastographic patterns of lymph nodes with the outcomes from endobronchial ultrasound-guided transbronchial needle aspiration in order to assess the usefulness of endobronchial ultrasound elastography for mediastinal and hilar lymph nodes.

Material and methods: A total of 52 lymph nodes were examined. Endoscopic ultrasound processor and a convex probe endobronchial ultrasonography were utilized to evaluate elastographic patterns that were categorized according to color distribution as follows: Type 1, which consists primarily of non-blue colors (green, yellow, and red); Type 2, which consists partly blue, partly non-blue (green, yellow and red); and Type 3, which consists of predominantly blue colors. The ultimate pathologic outcomes of the endobronchial ultrasound-guided transbronchial needle aspiration were compared to the elastographic patterns.

Results: On pathological evaluation of the lymph nodes, 11 were found to be benign and 41 were malignant. The lymph nodes that were classified as Type 1 on endobronchial ultrasound elastography were benign in 8/8 (100%); for Type 2 lymph nodes, 3/9 (33.3%) were benign and 6/9 (66.6%) were malignant; Type 3 lymph nodes were benign in 3/35 (8.5%) and malignant in 32/35 (91.4%). In classifying Type 1 as 'benign' and Type 3 as 'malignant,' the sensitivity, specificity, positive predictive value and negative predictive values were 85.3%, 81.8%, 94.59%, and 60%, respectively.

Conclusions: It is possible to predict nodal metastases during endobronchial ultrasound-guided transbronchial needle aspiration using the noninvasive endobronchial ultrasound elastography of mediastinal and hilar lymph nodes.

Keywords:- EBUS, Elastography, Lymph Nodes, Strain Ratio

INTRODUCTION

Neoplastic tissue usually shows higher cellularity and vascularity, which results in stiffer tissue, compared to normal structures [1]. The idea to use tissue stiffness as a novel diagnostic imaging tool originated in breast cancer diagnosis [2]. Tissue stiffness has also been used to measure elasticity in thyroid and liver disease.[3-6] The initial technology of imaging elasticity was first reported in 1991, and it was used to visualize the tissue strain that is caused by compression of probe [7].

Tissue stiffness is estimated by measuring the strain of the tissue in response to mechanical stress, either by local compression or vibration.Because harder tissues are less deformable than softer tissues, compression of the surrounding structures causes a deformation or strain effect that is inversely related to the hardness of the diseased tissue. We may figure out the tissue stiffness by comparing the amount of change between the region of interest (ROI) and its uncompressed state. The ultrasonic imaging technique known as EBUS elastography transforms the data on tissue stiffness into a colored image and displays it in color. For instance, the color for stiffness is blue and the color for softness is red.

Lung cancer is one of the most common malignant tumors and the leading cause of cancer death, with a 5-year survival rate of only 16%.[8] Correct diagnosis and staging are essential for lung cancer treatment. As a cutting-edge technique for lung cancer staging, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has been employed. Under the guidance of ultrasound images, the safety, and accuracy of TBNA have been greatly improved.[9] Consequently, EBUS-TBNA has been recommended as an important tool for lung cancer staging by the National Comprehensive Cancer Network (NCCN).[10] Ultrasound elastography technology has gradually been applied to the clinical setting.[11]

The aim of this study was to evaluate the elastography patterns of benign and malignant lesions based on the outcomes of EBUS-TBNA and to determine whether or not EBUS elastography may be employed for the noninvasive distinction of benign and malignant thoracic lymph nodes as a guide for EBUS-TBNA.

PATIENTS AND METHODS

Patients

The role of elastography and other sonographic features of

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CP-EBUS in diagnosing intrathoracic lymphadenopathy was studied at a clinical centre for pulmonary medicine at King George Medical University. Patient enrolment was prospectively performed from December 2021 to September 2022. EBUS elastography and EBUS-TBNA were performed based on the following conditions: (1) enlarged mediastinal/hilar LNs (at least 1 node >1 cm in the short axis) based on computed tomography (CT) or positive intrathoracic LNs detected on positron emission tomography (PET) (defined as standardized uptake value >2.5); (2) clinical and radiological features suspicious for malignancy or benignity, and pathological confirmation was clinically required to rule out other diseases or support systemic treatment of intrathoracic disease; (3) no contraindication to the procedure.

Written informed consent was obtained from each patient prior to performing endobronchial ultrasound. This study was approved by Institutional Ethics Committee,King George's Medical University,Lucknow.

Instruments and procedure

All EBUS procedures were performed under conscious sedation with injection midazolam and injection fentanyl. It used EB-1970UK linear ultrasound bronchoscopes (Pentax, Tokyo, Japan). Real-time EBUS B-mode and elastography with strain ratio measurements were performed using Diagnostic Ultrasound Scanner model EZU-AK1E (Hitachi, Tokyo, Japan).

B-mode EBUS characteristics

Based on previous studies of EBUS B-mode and vascular patterns on Doppler [12,13,14,15], malignant LNs characteristics were described according to the following characteristics: short axis with a diameter >1 cm; round shape; heterogeneous echogenicity; absence of central hilar structure (CHS); distinct margin and nonhilar perfusion of vascular pattern including central, capsular, and mixed. In this study a size of greater than 1 cm, distinct boundary, heterogeneous echogenicity and coagulation necrosis were considered to be signs of malignant infiltration of the lymph node.

EBUS Elastography

Elastography was performed on all lymph nodes that were candidates for EBUS-TBNA. After recording of the ultrasound image characteristics in B-mode, the procedure was switched to elastography mode. The entire lymph node and surrounding healthy tissue were scanned. Based on the compressive action produced by the pulsation of vessels in the thoracic cavity and respiratory movement, elastographic images were created. Comparing the scanned area's tissue to the tissue around it allowed for the reconstruction of its elasticity; observations were then converted into a color signal that was superimposed over the B-mode image. The colors associated with hard, intermediate, and soft tissues were blue, green, and yellow/red, respectively. Elastographic and B-mode images were simultaneously displayed side-by-side on the monitor. According to the prominent colors and how they were distributed inside the target lymph node, elastographic patterns were reported. An elastographic signal quality rating scale from 1-3 was used to describe the image. The following grading standard was used: (A) Predominantly non-blue (green, yellow and red) (Type 1). (B) Partly blue, partly non-blue (green, yellow and red) (Type 2). (C) Predominantly blue (Type 3). [16]

Fig 1:Predominantly non-blue [Type 1] Fig 2:Partly blue partly non-blue[Type 2Fig 3:Predominantly blue[Type 3]

The image on the right displays EBUS scanning on B-mode. On the left is a superimposed elastographic image with color scale based on tissue elasticity (the hardest tissues appear as blue and the softest tissues appear as red).

Calculation of strain ratio

The strain ratio was only measured when good contact and appropriate compression of the transducer were achieved, as indicated by the elastography image on the ultrasound processor. The largest possible area of the node was outlined from the superimposed elastography image; the same procedure was performed on a similar-sized area that was surrounded by apparently normal tissue. The strain of each area was quantitatively measured by the ultrasonic processor, and the strain ratio between the two areas was computed. Before EBUS-TBNA, the strain ratio was recorded at least three times. The mean of these recordings were determined.

EBUS-TBNA and final diagnosis

Following elastography, EBUS-TBNA using a Cook 22 gauge needle (Cook Ireland Limited, Limerick, Ireland) was carried out. Five to seven passes were obtained, and histological and cytological samples were collected and sent to the laboratory for subsequent analysis by pathologists who were blinded to the elastography results. A favorable outcome was defined as a conclusive diagnosis of cancer from the EBUS-TBNA specimens. No clear evidence of malignancy or inadequate specimen by EBUS-TBNA was considered a negative result.

STATISTICAL ANALYSIS

The statistical data analysis was performed using the Statistical Package for Social Sciences with SPSS software (Version 26.0, SPSS Inc., Chicago, Illinois, USA).Descriptive statistics for demographic and clinical variables were calculated using mean standard deviation and frequency. The diagnostic accuracy of strain ratio was compared with conventional EBUS-TBNA(gold standard) using receiver operating characteristic curve followed by determination of AUC,sensitivity,specificity,PPV and NPV. ROC curve was constructed for analysing sensitivity,specificity,PPV and NPV of strain ratio,elastography with other EBUS B-mode features.Probability(p) was calculated to test statistical significance at 5% level of significance($p<0.05$).

RESULTS

Patient and lymph nodes characteristics

EBUS elastography was performed on 52 lymph nodes at different lymph node stations in 30 patients (19 male and 11 female) with an average age of 59.5 (± 6.0) years. Twenty-three patients had a final diagnosis of lung cancer (11 adenocarcinoma, 7 squamous cell carcinoma, 3 small

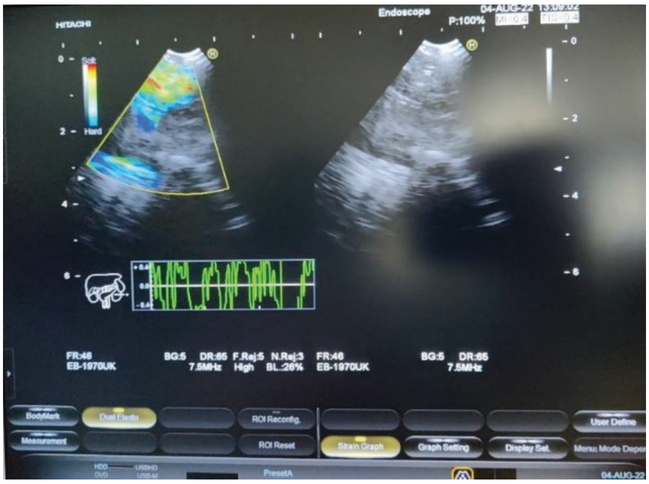
Figure-1: Predominantly non-blue [Type 1]

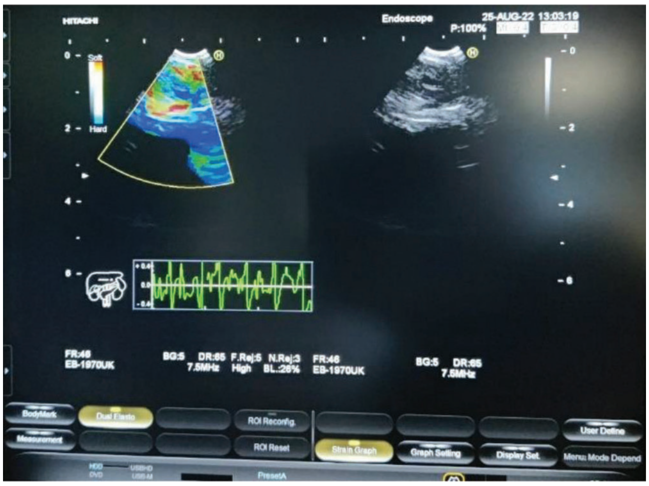
Figure-2: Partly blue partly non-blue [Type 2]

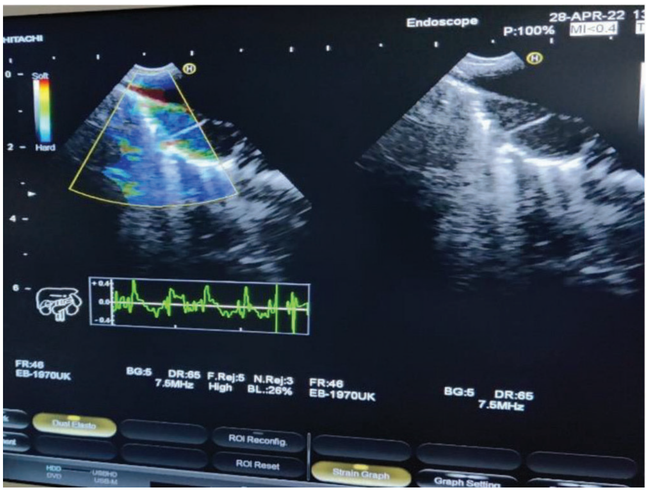
Figure-3: Predominantly blue [Type 3]

cell carcinoma and 2 poorly differentiated lung carcinoma); 7 patients had benign diagnoses at the end of the study (3 post-tuberculotic changes, 2 pneumonia/lung abscesses and 2 sarcoidosis). Among the observed lymph nodes, 9 were located in group 2R, 12 in groups 4R and 4L, 17 in group 7 and 14 in groups 10R and 10L. The clinical characteristics of the 30 study patients were summarized in Table 1.

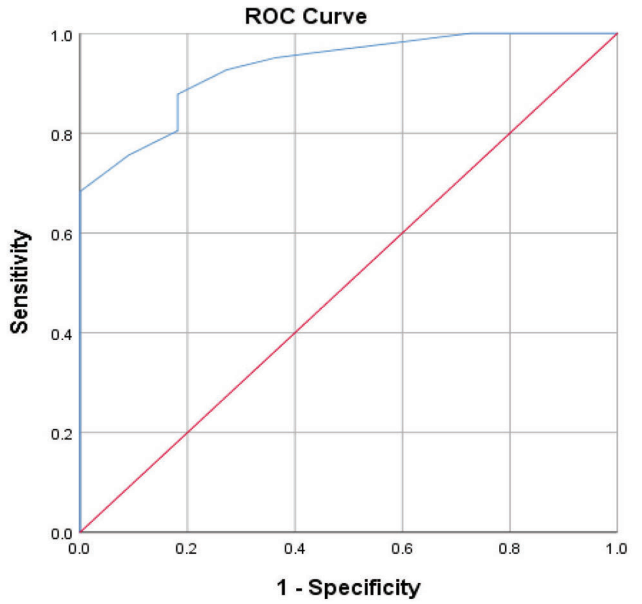

Figure-4: Receiver operating characteristic curve for elastography strain ratio

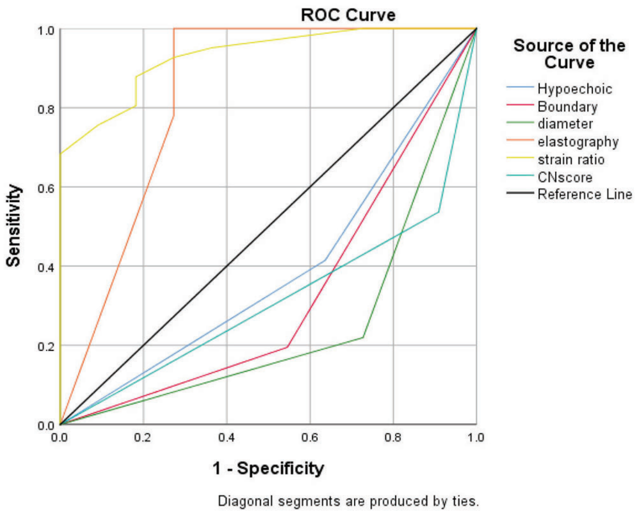

Figure-5: ROC curve for comparison of strain ratio, elastography grading score and EBUS B-Mode characteristics

Correlation of elastography grading score and strain ratio between malignant and benign lymph nodes

Out of 52 lymph nodes included in this work, 41 malignant and 11 benign lymph nodes were confirmed by pathological diagnosis. The elastography grading score was higher in the malignant lymph node group than in the benign lymph node group (2.78± 0.419 vs. 1.55± 0.934, *P*= 0.001). The strain ratio of malignant lymph nodes was significantly higher than that of their benign counterparts (17.34 ± 4.67 vs. 8.45 ± 3.45, *P*=0.0001). The strain ratio for malignant and benign lymph nodes was confirmed to be positively correlated with the elastography grading score (r = 0.683, *P*= 0.0001).

Diagnostic value of elastography strain ratio

The ROC area under the curve for the strain ratio was 0.931 (95% confidence interval [CI] 0.860-1.000, p < 0.0001; Figure 4). The optimal cut-off point for distinguishing malignant and benign lymph nodes, determined by a ROC sensitivity/specificity decision plot was at the strain ratio of 8.5 (Figure 5). Strain ratio values of 8.5 or higher represented the probability of malignant involvement with an accuracy of 86.25%,sensitivity 95.1%, specificity 63.6%, PPV 90.02%, NPV 77.9%.

Comparison between elastography strain ratio vs. EBUS B-mode features for benign and malignant lymph nodes

The ability of elastography strain ratio to differentiate between malignant and benign lymph nodes was compared with the EBUS B-mode features of the same lymph nodes; the data are shown in Table 2.The AUCs(area under curve) obtained from receiver operating characteristic curve for hypoechoic, distinct boundary, short diameter ≥1 cm, coagulation necrosis score,elastography grading score, and strain ratio were 0.389, 0.325, 0.246, 0.314, 0.834, and 0.931, respectively [Figure 5]. Elastography strain-ratio assessment was more accurate than any other lymph node characteristic assessed using EBUS B-mode criteria[Table 2].

DISCUSSION

The use of mediastinoscopy and EBUS-TBNA for mediastinal staging and pathological examination has been recommended in NCCN guidelines as both methods reveal no significant statistical differences in terms of diagnostic sensitivity and accuracy of judging mediastinal lymph node metastasis.[17] EBUS-TBNA plays a crucial role in mediastinal staging as needle aspiration guided by ultrasound has greatly increased the positive rate of mediastinal lymph node biopsy.[18]

The accuracy of conventional ultrasound image characteristics like shape of lymph node, heterogeneous echoes, edge clarity, and coagulation necrosis in the diagnosis of malignant lymph nodes is not particularly high, and the subjective judgment of the technician is often required.[19]. In our study, the most commonly used criteria for differential diagnosis in the decreasing order of importance according to diagnostic accuracy are as follows: coagulation necrosis (80.76%), short axis diameter >1cm and hypoechoic characteristics have same accuracy (66.67%) followed by distinct boundary. It appears that coagulation necrosis score is the best predictor. However, it has a limited sensitivity of 46.34%.

Elastography is the simplest qualitative method for assessment of lymph nodes, since colour pattern is a visualized diagnostic standard that is easy to perform. This study described 3 elastographic patterns (predominantly non-blue, predominantly blue, and partly blue, partly non-blue). The findings revealed that non-blue nodes were benign with 100% probability, while blue ones had a 91.4% chance of being malignant. However, indeterminate mixed-pattern nodes were equivocal to be benign or malignant. These findings are consistent with data published by Sun group[20].

Although elastography is a simple method of assessing lymph node status,it is subjective in nature and therefore leads to interobserver bias.To minimize this, elastography is being compared to an objective method of measuring tissue stiffness, namely strain ratio. With EBUS elastography, sensitivity and specificity were 95.1% and 63.6%, respectively, using a strain ratio cut-off of 8.5 for malignancy. The strain ratio displayed the highest ROC AUC when compared to all of the traditional EBUS criteria examined. The diagnostic value of the elastography grading score reduced in comparison to the strain ratio. The strain ratio between cancerous and benign lymph nodes and the elastography grading score were

1) Gender	
Male	19
Female	11
2) Age (years)	59.5±6.0
3) Ln location	
Upper paratracheal(2R)	9
Lower paratracheal(4R,4L)	12
Subcarinal(7)	17
Hilar (10R,10L)	14
4) Mean in size (mm)	13±2.16
5) Pathology	
Malignant	41
Squamous cell carcinoma	13
Adenocarcinoma	20
Small cell carcinoma lung	05
Poorly differentiated lung cancer	03
Benign	11

Table-1: Patient and lymph node characteristics of 30 patients. LN - lymph node; 2R - Right upper paratracheal; 4r & 4l - Right and left lower paratracheal; 10R & 10L - Right and left hilar

Ultrasound Parameters	Hypoechoic	Distinct Boundary	Short Diameter	CNS	Elastography Score	Strain Ratio
Specificity	63.6% (7/11)	54.54% (6/11)	72.72% (8/11)	90.9% (10/11)	81.8% (9/11)	81.8% (9/11)
Sensitivity	58.5% (24/41)	80.4% (33/41)	78.04% (32/41)	46.34% (19/41)	85.3% (35/41)	87.8% (36/41)
PPV	85.7% (24/28)	86.4% (33/38)	91.42% (33/35)	95.0% (19/20)	94.59% (35/37)	94.73% (36/38)
NPV	29.1% (7/24)	42.8% (6/14)	47.05% (8/17)	31.25% (10/32)	60.0% (9/15)	64.0% (9/14)
Accuracy	73.07% (38/52)	71.15% (37/52)	73.07% (38/52)	80.76% (42/52)	84.61% (44/52)	86.5% (45/52)

Table-2: Diagnostic value of different ultrasound parameters CNS-Coagulation necrosis score strongly associated.

The main purpose of elastography is to measure the tissue hardness. The strain ratio within the node may, however, drop when the "softer" components of the node are evaluated,like central necrosis and vascular invasion ultimately influencing the application of elastography techniques. For instance, 3 nodes had an elastography strain ratio that gave a false negative result out of the 41 pathologically confirmed malignant cases included in this work. Additionally, lymph node calcification may make them harder. This phenomenon might be the cause of the tuberculosis patients' considerably elevated lymph node strain ratio.

The elastography grading score can be affected by subjective factors because it is usually recorded according to the elastogram color distribution characteristics.[21] Since interobserver variability does not affect the strain ratio, it can be considered an objective measurement. However, technical issues that can challenge ultrasound elastography examinations include breathing exercises and adjacent vascular pulsations that produce certain compressive displacements[22]. As a result, it is difficult to obtain elastic recordings or diagnoses that are exactly the same for two inspections. Choosing image frames with a pressure curve and amplitude that are comparatively stable and repeated and dynamic recording to reduce errors are two possible methods.

In conclusion, our research shown that EBUS elastography, particularly the strain ratio, is more precise than conventional EBUS imaging for differentiating between benign and malignant mediastinal lymph nodes of lung malignancies. The positive diagnosis rate of TBNA is increased by EBUS elastography, and the procedure can be completed faster and with fewer biopsies.

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