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Endobronchial Ultrasound Elastography for Differentiating Benign and Malignant Lymph Nodes

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Endobronchial ultrasound, Elastography, Bronchoscopy

Abstract
Background: Endobronchial ultrasound elastography that provides information on tissue stiffness may help distinguish malignant from benign mediastinal and hilar lymph nodes. ***Objectives:*** In this prospective trial, we assessed the diagnostic value of elastographic images and the interobserver agreement in its evaluation. ***Method:*** Elastographic images from 77 lymph nodes in 65 patients were reviewed by 3 pneumologists. The elastographic image was classified based on the predominant colour: predominantly green, intermediary, and predominantly blue. With 2 or 3 interobserver matches, the corresponding elastographic image was correlated with the pathological result obtained from endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and/or other invasive procedures. ***Results:*** All 3 reviewers had agreement in classifying elastographic images in 45% (35/77). Overall, the interobserver agreement among the 3 readers for classifying elastographic pattern was found to be moderate (Fleiss Kappa index = 0.519; 95% CI = [0.427; 0.611]). On cytological/histological evaluation, 55 lymph nodes were malignant and 22 were benign. In classifying "green" as benign and "blue" as malignant, the sensitivity and specificity were 71% (95% CI = [54%; 85%]) and 67% (95%-CI = [35%; 90%]), respectively. ***Conclusions:*** Elastography will not replace invasive EBUS-TBNA due to a moderate interobserver agreement and insufficient sensitivity and specificity. However, elastography will, maybe, present an additional feature to identify malignant lymph nodes in the context of clinical, radiological, and cytological results.

Introduction

Precise lung cancer staging is crucial as it determines therapeutic strategy and prognosis. Besides assessment for distant metastases, accurate mediastinal staging is mandatory for planning optimal treatment [1]. Current guidelines recommend an invasive mediastinal staging in patients with enlarged lymph nodes in CT and/or positron emission tomography-positive lymph nodes. Thereby, endosonographically guided needle biopsy is the first choice, since it has a high sensitivity to confirm mediastinal nodal metastases. In case of cytological neg-

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ative results, subsequent surgical staging is recommended as surgical staging procedures have a lower post-test probability of missing nodal metastases compared to needle biopsy [2]. Furthermore, mediastinal staging by endosonography is mandatory in patients without nodal involvement in imaging techniques but with N1 nodes, central tumours, tumours >3 cm, and positron emission tomography-negative tumours. If negative, a subsequent mediastinoscopy may be considered. However, it must be taken into account that surgical procedures are associated with a higher rate of serious complications compared to needle techniques [3]. This fact stimulates the search for additional endosonographic features that minimizes the post-test probability for missing nodal metastases by needle aspiration, so that a subsequent surgical staging is superseded. Ultrasound elastography as non-invasive method has been shown to support differentiation between malignant and benign lymph nodes. By analysing elastography colour distribution and/or calculation of the strain ratio, malignant lymph nodes may be distinguished from benign nodes [4–12]. In this prospective trial, we aimed to assess the utility of the elastography colour pattern for distinguishing malignant and benign lymph nodes and the interobserver agreement in its visual evaluation, in patients with enlarged lymph nodes on CT scan.

Methods

This prospective single-arm trial investigated the interobserver agreement, sensitivity, and specificity of endobronchial elastography in patients with radiological evidence of hilar and/or mediastinal lymph node enlargement. The local ethics committee of Heidelberg approved the protocol of this trial (S-560/2013).

Study Subjects

Patients with enlarged hilar and/or mediastinal lymph nodes on CT scan with suspicion of malignant or benign diseases were enrolled in this prospective trial. Eligible patients were at least 18 years of age, had an indication for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), and had given informed consent prior to bronchoscopy.

Bronchoscopic Procedure and Elastography Evaluation

All bronchoscopic procedures were performed in the Thoraxklinik, University of Heidelberg, Germany. According to the institutional standard, all patients underwent combined rigid and flexible bronchoscopy under general anaesthesia. After identifying enlarged lymph nodes by using the real-time EBUS B-modes of a linear ultrasound bronchoscope, elastographic images that result from vascular pulsation and respiratory movements were obtained using the "freeze function." Of each lymph node, 2–4 elastographic images were captured as JPEG images. Afterwards, the lymph node was punctured by using a 21-gauge needle and cytological smears and cellblocks were prepared. The pathologist was blinded to the elastographic colour pattern.

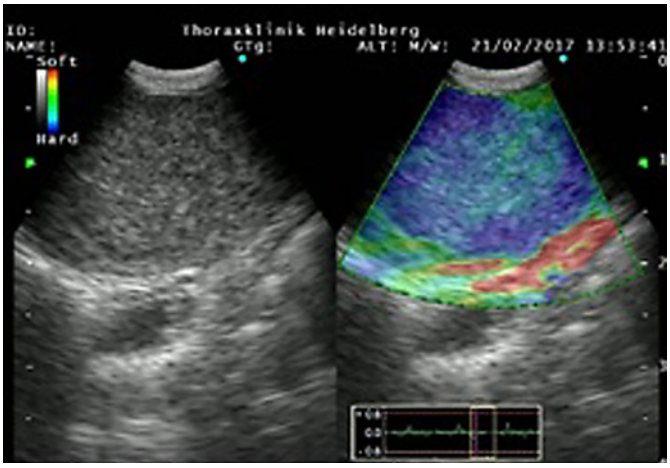

Fig. 1. Endobronchial elastography shows a predominantly blue pattern.

Interobserver Agreement

Following the procedure, the elastographic images of each lymph node were reviewed post hoc by 3 pneumologists independently. All readers were similarly experienced in ultrasound techniques and bronchoscopic procedures. They were unblinded to the clinical data of the patient but blinded to the pathological result.

The elastographic patterns were classified qualitatively based on colour distribution as follows: predominantly green, intermediary (part blue, part non-blue), and predominantly blue (Fig. 1-3). If 3 or 2 readers agreed in 1 elastography type, this pattern was used to calculate the sensitivity and specificity. In cases all 3 readers disagreed, the intermediary pattern has been used for the correlation with the cytological/histological result.

Definitive Diagnosis

If EBUS-TBNA cytology revealed malignant cells, malignancy was accepted as a definitive diagnosis. Final diagnosis of sarcoidosis was made with cytological evidence of non-caseating granulomatous inflammation in the context of the clinical history and the radiological examination of the patient. If only lymphocytes were present in the cytology specimen, benign disease was confirmed by surgical treatment including lymph node dissection and/or clinical long-term follow-up. In case of absent cytological/histological confirmation and insufficient clinical follow-up, subjects/lymph nodes were excluded from the analysis.

Statistical Analysis

Data were given as mean values and ranges for continuous parameters, as well as absolute and relative frequencies for categorical parameters. Sensitivity and specificity were calculated together with 95% exact confidence intervals. The degree of interobserver agreement was determined by assessment of the Fleiss kappa index (KI) [13] (KI < 0, poor agreement; KI 0.0–0.20, slight agreement;

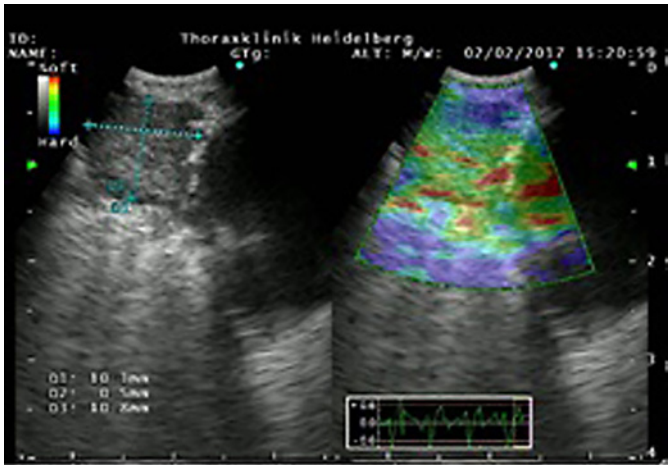

Fig. 2. Endobronchial elastography shows an intermediary pattern.

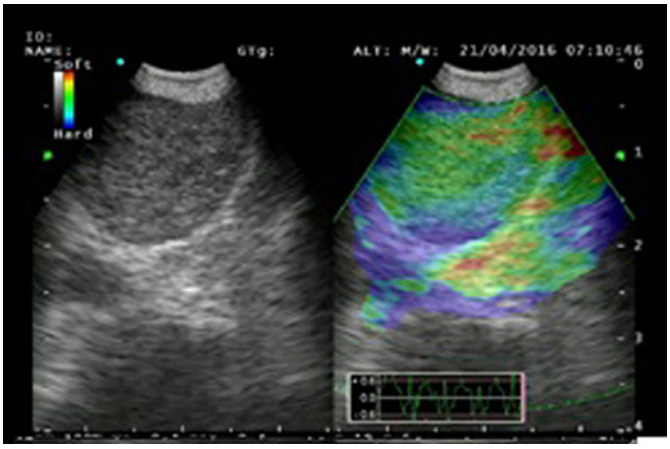

Fig. 3. Endobronchial elastography shows a predominantly green pattern.

KI 0.21–0.40, fair agreement; KI 0.41–0.60, moderate agreement; KI 0.61–0.80, substantial agreement; KI 0.81–1.0, almost perfect agreement) with a 95% confidence interval. This statistical analysis was carried out with R v3.4.2 (http://r-project.org) using the *irr* and the *binom* package.

Results

Patients and Final Diagnosis

In this prospective trial, endobronchial elastography and EBUS-TBNA were performed on 77 lymph nodes in 65 patients (53.2% male, mean age 63 years, range 52–82 years) with suspected diagnosis of lung cancer (n = 47), cancer recurrence (n = 2), metastases of extrathoracic malignancy (n = 1), sarcoidosis (n = 10), or lymphadenopathy of unclear origin (n = 3) (Table 1). In 2 patients with proven lung cancer, EBUS-TBNA was performed for mediastinal staging. Lymph nodes were located in 7 (n = 40), 4R (n = 10), 4L (n = 4), 10R (n = 2), 10L (n = 1), 11R (n = 8), 11L (n = 10), 12R (n = 1), and 12L (n = 1). In 2 out of the 65 enrolled patients, a suspicious mass was found in 10L and 11R, respectively, indicating a centrally located primary lung cancer. Final diagnosis was established by EBUS-TBNA alone in 59 subjects, EBUS-TBNA and subsequent surgical intervention in 9 patients, surgical lymph node dissection alone (negative cytology results obtained by EBUS-TBNA) in 7 cases, and EBUS-TBNA and clinical follow-up in 2 patients. On cytological/histological evaluation, 55 lymph nodes were malignant and 22 were benign. The pathological results are shown in Table 1.

Table 1. Pathological result

Cytological/histological result	
Malignant (n = 55)	
Adenocarcinoma	21 (38%)
Squamous cell carcinoma	14 (25%)
Non-small cell carcinoma	9 (16%)
Small cell carcinoma	8 (15%)
LCNEC	1 (2%)
Non-Hodgkin lymphoma	1 (2%)
Metastasis of breast cancer	1 (2%)
Benign (n = 22)	
Sarcoidosis	16 (73%)
Unspecific	6 (27%)

Table 2. Distribution of the elastographic pattern according to the final pathological result

	Elastography		
	predominantly blue	intermediary	predominantly green
Pathological result			
Benign	4	10	8
Malignant	25	20	10

Interobserver Agreement

The elastographic images of each lymph node obtained prior to EBUS-TBNA were independently reviewed by 3 pneumologists who were unblinded to the

patient's clinical data but blinded to the cytological/histological result. The lymph nodes were classified as "predominantly blue," "intermediary," and "predominantly green" in 29, 30, and 18 cases, respectively. All 3 reviewers had agreement in classifying elastographic image in 45% (35/77). The highest agreement between observers was found in case of malignancy. Overall, the interobserver agreement among the 3 readers for classifying elastographic pattern was found to be moderate (KI = 0.519, 95% CI = [0.427; 0.611]).

Sensitivity and Specificity

The elastographic patterns were compared with the final cytological results from EBUS-TBNA and/or subsequent surgical lymph node dissection. The lymph nodes that were classified as "predominantly blue" (n = 29) by at least 2 readers were found to be malignant in 86.2% (25/29) and benign in 13.8% (4/29). The 30 lymph nodes with an "intermediary" elastographic pattern were malignant in 66.7% (20/30) and benign in 33.3% (10/30). Lymph nodes presented as elastographic pattern "predominantly green" (n = 18) were malignant in 55.6% (10/18) and benign in 44.4% (8/18). Table 2 shows the distribution of the elastographic patterns according to the final pathological result. In classifying "predominantly blue" as "malignant" and "predominantly green" as "benign," the sensitivity and specificity were 71% (95% CI = [54%; 85%]) and 67% (95% CI = [54%; 85%]), respectively.

Discussion

Endobronchial elastography that evaluates tissue elasticity has been shown to be a feasible and reliable technique for classifying enlarged hilar and mediastinal lymph nodes [4–8]. Izumo et al. [4] classified the qualitative elastographic findings into 3 patterns according to the dominant colours within the target lymph node: predominantly blue, intermediary, and predominantly green. Predominantly blue is considered to be malignant and predominantly green is indicative for benignancy. Rozman et al. [5] introduced the strain ratio measurement, whereby a strain ratio ≥8 was associated with a high probability of malignancy. Thus, elastography may support differentiation of benign and malignant lymph nodes with greater accuracy than conventional EBUS modalities. Various trials reported a sensitivity of 72–100% and a specificity of 65–92% of the colour-based qualitative elastography and/or the strain ratio-based quantitative elastography in predicting benignancy/malignancy [4–12].

In the current analysis, the sensitivity and specificity of the qualitative elastography were found to be 71 and 67%, respectively. These moderate results indicate that the use of elastography alone for predicting malignancy is not sufficient. The accuracy of the subjective quantitative colour-based elastography may be improved by further elastography methods such as the strain histogram, the stiff area ratio, or the strain ratio [10, 12]. Furthermore, the elastography may be combined with other sonographic findings [7, 12]. In 1 trial, B-mode sonography and elastography were evaluated for 228 lymph nodes [12]. The sonographic features of B-mode imaging and the strain ratio-based elastography revealed a sensitivity of 94 and 72%, respectively, and a specificity of 77 and 84%, respectively. Combining these 2 methods resulted in a sensitivity of 94% and a specificity of 89% and thus in a higher diagnostic yield than either modality alone for predicting benign and malignant lymph nodes.

Qualitative elastography is a subjective measurement, so that the elastography result may be influenced by unconscious bias and thus may generate misleading results. In the current trial, only a moderate interobserver agreement was found, which implies that differentiation between the 3 qualitative elastographic patterns is not straightforward. This finding is contrary to an almost perfect interobserver reliability with a kappa value of 0.88, which was found in a previous published trial [10]. It is noteworthy that in the trial published by Korrungruang et al. [10], only 3% of the lymph nodes were classified as "intermediary" by 2 reviewers in contrast to the finding in our study, in that 39% of the lymph nodes/lesions were classified as "intermediary" in the elastographic image by at least 2 of 3 reviewers. In earlier studies, authors reported an "intermediary" elastography pattern in 19–53% of the lymph nodes [4, 7]. This "intermediary" elastography type is inconclusive and does not give any additional information about the dignity.

One limitation of the study is that the patients were not consecutively enrolled in this prospective trial, which may lead to a selection bias. However, this study focused on the evaluation of the interobserver agreement of 3 blinded readers for classifying elastographic images, which may not be affected to a great extent by the sample technique.

Another limitation of the study is that only the quantitative elastography was used to assess the interobserver variability of endobronchial elastography. It may be assumed that the interobserver variability of qualitative

elastography may be reduced by combing this qualitative method with quantitative strategies as assessing the strain histogram, the stiff area ratio, or the strain ratio. However, also these measurements should repeated several times for 1 lymph node, and the median value should be selected as studies revealed a significant intraobserver variability of these measurements [10]. In this study, we did not reveal the intraobserver variability, but the bronchoscopists reported a selection bias of the still image and lack of reproducibility in some cases.

In summary, the interobserver variability of elastography pattern of hilar and mediastinal lymph nodes is not negligible and should be taken into account. Qualitative elastography can give additional information but does not allow reliable discrimination between malignant and benign mediastinal or hilar lymph nodes.

Statement of Ethics

The protocol of this trial was approved by the local ethics committee of Heidelberg (S-560/2013).

Conflict of Interest Statement

D.G.: Lecture and travel fees from Pulmonx, Olympus, Chiesi, Boehringer Ingelheim, Novartis, Astra Zeneca, Mundipharma, Berlin Chemie and Grifols. K.K.: No conflicts of interest. N.S.: No conflicts of interest. P.H.: No conflicts of interest. J.K.: No conflicts of interest. R.E.: Lecture fees from Olympus, Pulmonx, Broncus and Uptake Medical. F.J.F.H.: Fees for lectures and advisory boards from Astra, Allmirall, Berlin Chemie, Boehringer, Roche, GSK, Pulmonx, BTG, Olympus, PneumRx, Boston Scientific, Medupdate, Grifols, CSL Behring, Omniamed, Lilly, Novartis, Teva, Uptake and Vital Air.

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