Diagnostic value of endobronchial ultrasound elastography combined with rapid onsite cytological evaluation in endobronchial ultrasound-guided transbronchial needle aspiration

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Abstract

Background: Endobronchial ultrasound (EBUS) elastography has been applied in EBUS-guided transbronchial needle aspiration (EBUS-TBNA) to identify malignant lymph nodes based on the tissue stiffness. Rapid onsite cytological evaluation (ROSE) has been widely used for onsite evaluation of the adequacy of the samples and guiding the sampling during EBUS-TBNA. The aim of the study is to investigate the diagnostic value of combined EBUS elastography and ROSE in evaluating of mediastinal and hilar lymph nodes status.

Methods: A retrospective chart review was performed from December 2018 to September 2020. Patients' demographic, EBUS elastography score, ROSE, pathologic and clinical outcomes were collected. The EBUS elastography scores were classified as follows: Type 1, predominantly non-blue; Type 2, partially blue and partially non-blue; Type 3, predominantly blue. Receiver operating characteristic (ROC) curve was used to compare the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio among EBUS elastography, ROSE, and EBUS combined with ROSE groups for evaluation of malignant lymph nodes.

Results: A total of 247 patients (345 lymph nodes) were included in our study. The sensitivity and specificity of EBUS elastography group in the diagnosis of malignant lymph nodes were 90.51% and 57.26%, respectively. The sensitivity and specificity in the ROSE alone group were 96.32% and 79.05%, respectively. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of EBUS elastography combined with ROSE group were 86.61%, 92.65%, 11.78, and 0.14, respectively, and the area under curve was 0.942.

Conclusions: The combination of EBUS elastography and ROSE significantly increased the diagnostic value of EBUS-TBNA in evaluating mediastinal and hilar lymph nodes status.

Background

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a new technique developed in 2002. Currently, the EBUS-TBNA has been highly recommended by National Comprehensive Cancer Network (NCCN) and American College of Chest Physicians (ACCP) for the diagnosis and preoperative staging in patients with lung cancer. Ultrasonography has been widely applied for identifying malignant lymph nodes status and guiding lymph node aspiration. However, conventional ultrasonography does not show particularly high accuracy in identifying the malignant lymph nodes (Garcia-Olive et al. 2012). Elastography is a real-time imaging technique to identify malignancy based on the tissue stiffness. The relative elasticity or stiffness of the tissue was determined by applying the stress to the tissue, causing the deformation of the tissue and the echo signals are converted to real-time images (Dietrich et al. 2014). Red signals indicate a low elasticity coefficient in tissues, while the blue signals demonstrate a high elasticity coefficient in tissues. Malignant tumors are usually hard tissues, thus, allowing the identification of malignant lesions by elastosonography (He et al. 2017). Recently,

ultrasound elastography has been widely applied in the diagnosis of breast cancer, prostate cancer, and fibrosis staging of liver (Barr et al. 2015; Good et al. 2014; Huang et al. 2020). Due to the characteristics of EBUS elastography for rapid identifying malignant mediastinal lymph nodes, EBUS elastography was also applied in EBUS-TBNA for better identifying the suspicious lesions. Mittal et al. mentioned that the sensitivity and specificity of EBUS elastography to identify malignant lymph nodes were 85.7%-100% and 66.7%-92.3%, respectively (Mittal et al. 2019).

During EBUS-TBNA, rapid onsite cytological evaluation (ROSE) has been widely used for evaluating samples, for example, guiding the following passes, identifying the proper location and determining the adequacy of the samples for further immunohistochemistry or next generation sequencing (NGS) (Sehgal et al. 2020). However, some studies showed that ROSE alone could not improve the diagnostic sensitivity of EBUS-TBNA (Sehgal et al. 2018).

Recently, ROSE has been used as an ancillary procedure in some EBUS elastography related studies, however the diagnostic values of combined EBUS elastography and ROSE are largely unknown (Gu et al. 2017; Huang et al. 2017). The aim of this study is to investigate the diagnostic value of combined EBUS elastography and ROSE in EBUS-TBNA.

Materials And Methods

Patients

A retrospective study was performed to identify patients underwent EBUS procedure due to the enlargement of mediastinal or hilar lymph nodes at our institution from December 2018 to September 2020. This study was approved by the Ethics Committee of ZhongDa Hospital, School of Medicine, Southeast University. A total of 247 patients were included in our study. Patients' demographic, pathologic features, and clinical outcomes were collected by chart review. All lymph nodes samples were divided into three groups: EBUS elastography, ROSE, and combined EBUS elastography and ROSE.

Patients results of routine blood test, chest high-resolution computerized tomography (CT) scan and electrocardiograms were reviewed before the procedure. Patients were required to fasting 6-8 hours before the procedure and patients' status were monitored by the anesthesiologist during the procedure. EBUS-TBNA was performed under conscious sedation combined with local anesthesia and the convex probe EBUS (BF-UC260F, Lympus, Japan) was inserted through the nose route. After identifying the lesion, the size of the lymph nodes and the distribution of the vessels were evaluated and the EBUS elastography images were analyzed by two pulmonologists individually. At least three passes were performed for each lesion with 15-20 aspirations. The 21G aspiration needles (NA-201SX-4022, Olympus® Corporation, Japan) were used for the aspiration.

EBUS elastography image analysis

Real-time EBUS B-mode was performed to evaluate the lesion and part of the normal tissue followed by elastography image analysis. During the procedure, the operator gently pressed the convex probe to perform elastography and the images were recorded for further analysis. The elastography images were divided into three categories: Type 1 (predominantly non-blue); Type 2 (partially blue and partially non-blue); and Type 3 (predominantly blue) as previously mentioned in Izumo et al's scoring system (Izumo et al. 2014) (Figure 1). After elastography image analysis, EBUS-TBNA aspiration was performed as usual. If the Type 2 elastography image was found in the lesion, the blue area is the preferred area for aspiration (Lin et al. 2019).

ROSE procedure and interpretation

ROSE interpretation was performed by a pulmonologist with at least one year experience in evaluating ROSE results without known the results of EBUS elastography image analysis. The specimens were collected and the smear was prepared as previously described. The remaining specimens were fixed in 10% formalin and sent to the Pathology Department for routine test. The Diff-Quick stain was used for rapid staining in ROSE according to manufacturer's instruction (Jain et al. 2018). Briefly, the slides were stained with solution A for 15- 20 seconds, followed by solution B for additional 15-20 seconds. The slides were then rinsed in tap water and dried by absorbent paper.

ROSE interpretation was performed according to the guidelines of the Papanicolaou Society of Cytopathology System for Reporting Respiratory Cytology. In general, the results were classified into five categories: 1. Non-diagnostic (unsatisfactory); 2. Negative for malignancy; 3. Atypical cells present; 4. Suspicious for malignancy. 5. Positive for malignancy. For the following studies, Categories 2 and 3 were defined as negative cases, while category 4 and 5 were defined as positive cases. Category 1 was not included in the following studies. The final diagnosis was based on the final pathological diagnosis.

Statistics

SPSS 22.0 (SPSS Inc., Chicago, IL, USA) statistical software was used for the statistical analysis. All quantitative data obtained are expressed as the mean $\pm$ standard deviation. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio of EBUS elastography, ROSE, and EBUS elastography combined with ROSE for detecting malignant lymph nodes were compared. Receiver operating characteristic (ROC) analysis was performed to determine the test performance of the different methods. A difference of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

From December 2018 to September 2020, a total of 247 patients were included in our study. Two patients were excluded from the final analysis due to the deficiency of the final pathological diagnosis. Patients'

characteristics and clinical information were summarized in Table 1. The mean age was 61.60 ± 11.85 years (ranging from 26-86 years) with a male dominant (male vs female: 149 vs 96). 148 cases were identified as positive for malignancy while 99 cases were identified as negative for malignancy (Table 2). A total of 345 aspirated lymph nodes were included in the cohort, including 254 specimens with EBUS elastography results and 268 specimens with ROSE results respectively. Among the 148 malignant cases, adenocarcinoma was the most common malignancy ($n=73$, 49.32%), followed by small cell carcinoma ($n=26$, 17.59%) and squamous cells carcinoma ($n=23$, 15.54%). While for benign cases, sarcoidosis ($n=36$, 36.36%), no abnormality identified ($n=35$, 35.35%) and inflammation ($n=16$, 16.16%) were the most common pathological diagnosis for EBUS-TBNA. One patient had small cell carcinoma and comorbid tuberculosis. Representative cases of benign and malignant cases were shown in Figure 2.

Table 3 summarized the first line treatment for 148 malignant cases. Among the 73 patients diagnosed with adenocarcinoma, 42 cases (58%) were sent for molecular testing by TBNA puncture, and epidermal growth factor receptor (EGFR) mutation was identified in 11 (26.2%) these cases, while ALK rearrangement was observed in 3 (4.8%) cases. As illustrated in Table 3, chemotherapy was still the most common first line treatment for patients with positive mediastinal or hilar lymph nodes.

Comparison of results among EBUS elastography, ROSE, and combined EBUS elastography with ROSE groups

As demonstrated in Table 4, the sensitivity and specificity of EBUS elastography alone in the diagnosis of malignant lymph nodes were 90.51% and 57.26% respectively. While the corresponding sensitivity and specificity in ROSE alone group were 96.32% and 79.05%, respectively. Interestingly, we observed that the sensitivity and specificity in the combined group were 86.61% and 92.65%, respectively with an increased area under the curve (AUC) of 0.942. Therefore, the combination of EBUS elastography and ROSE was found to have the best diagnostic value among the three groups (Table 4, Figure 3).

Discussion

EBUS-TBNA has become a mature interventional diagnostic procedure in clinical practice. Previous studies showed that no statistically significant difference was identified between EBUS-TBNA and mediastinoscopy in diagnostic sensitivity to evaluate malignant lymph nodes with previous imaging results indicating the enlargement of mediastinal and/or hilar lymph nodes or adjacent lesions in lungs (Figueiredo et al. 2020). However, compared to mediastinoscopy, EBUS-TBNA was a less invasive procedure with low costing and better tolerability for patients (Sampsonas et al. 2018; Verdial et al. 2020). Currently, EBUS-TBNA has gradually replaced mediastinoscopy and been recommended by multiple guidelines as the first choice for TNM staging in lung cancers.

To further improve the diagnostic sensitivity of EBUS-TBNA and decrease procedure-related complications, some studies were performed by analyzing lymph nodes' shape, echogenicity (homogeneous or heterogeneous), margin status, presence or absence of central hilar structure (CHS), short axis diameter, and coagulative necrosis under B-mode ultrasound to evaluate the lesions (Evison et

al. 2015; Fujiwara et al. 2010; Garcia-Olive et al. 2012). Even including multiple values, discrepancies still existed among different studies (Agrawal et al. 2020). So far, none of the EBUS features were proved to be consistently with the diagnosis of malignant lymph nodes. Thus, the real-time imaging technology, EBUS-elastography could be a new technique to solve these problems. The main mechanism of EBUS elastography is stiffer tissues have lower strain. In addition, compared to soft tissues, stiff tissues showed less deformation under pressure. EBUS-elastography converts the different echo signals into different real-time color images based on the stiffness of the tissue. Thus, the changing of color from red to blue indicates the tissue from soft to hard (He et al. 2017). Recently, EBUS elastography has been widely applied in the diagnosis of breast cancer, prostate cancer, liver disease, myopathies etc. (Berzigotti 2017; Janczyk et al. 2020; Kapetas et al. 2019; Wildeboer et al. 2020).

Endoscopic elastography has been well-developed recently and demonstrated its superiority in lesion evaluation compared to the conventional ultrasound especially in the esophageal endoscopic ultrasound (EUS). Previous study has shown that the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of endoscopic elastography in diagnosing pancreatic solid tumor were 93%, 66%, 92%, 69%, and 85%, respectively (Fusaroli et al. 2012), while the sensitivity and specificity in differentiating benign versus malignant peripancreatic lymph nodes were 91.8% and 82.5%, respectively (Giovannini et al. 2009). Recently, endoscopic elastography was also developed in the EBUS. Multiple studies have indicated that EBUS elastography could be widely applied in differentiating benign versus malignant mediastinal lymph nodes (Lin et al. 2019; Sun et al. 2017; Trosini-Desert et al. 2019). Izumo et al. (Izumo et al. 2014) performed a retrospective study including 75 mediastinal lymph nodes and their study indicated that the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of EBUS elastography in diagnosing malignant lymph nodes were 100%, 92.3%, 94.6%, 100%, and 96.7%, respectively. The negative predictive value of 100% demonstrated that EBUS elastography could decrease the number of unnecessary aspiration and the total examination time. Controversially, other studies showed sensitivity or specificity of EBUS-elastography in the diagnosis of malignant lymph node were around 75% - 87% or 65%-68% (Caglayan et al. 2020; Fournier et al. 2019). The discrepancy could be partly due to the different way to interpret the image results in EBUS-elastography. For example, in Izumo et al's study, lymph nodes that appeared partially blue or non-blue on elastography images were not included in the statistical analysis. Thus, some modifications have been applied to the observation method of elastography, eg. subjective quantification method. The subjective quantification method includes the use of the stiffness ratio, strain histogram, stiffness area ratio, or strain ratio to predict the elasticity characteristics of the lesion (Fujiwara et al. 2019; Korrunguang and Boonsarngsuk 2017; Nakajima et al. 2015; Verhoeven et al. 2019). Taiki et al. achieved a sensitivity of 83.0% and a specificity of 96.2% by combining B-mode ultrasound and elastography in prediction of nodal metastasis(Fujiwara et al. 2019). However, all these methods need additional software for image processing and calculations, which are time consuming. Additionally, it needs extra training and experience for evaluating the results of B-mode ultrasound. Therefore, Izumo's scoring method was the most widely used method in clinical practice which was also the method applied in our study. Consistent with previous studies with a sensitivity in EBUS-elastography ranging from 71% - 90.6%, our study

showed a sensitivity of 90.5%. However, the corresponding specificity was only 57.3% in our study which was lower than other studies (67%-82.6%) (Fournier et al. 2019; Gompelmann et al. 2020; Lin et al. 2019). We believe that the discrepancy could be due to the multiple factors related to the final results during the EBUS-elastography, eg. calcification or necrosis in the lymph nodes (He et al. 2017). False positive results have been reported in previous studies, mostly due to the increased stiffness in tuberculosis, pneumoconiosis, or sarcoidosis (Abedini et al. 2020; Dong et al. 2018; Trisolini et al. 2020) (Livi et al. 2019). In our study, we observed that 6 cases had blue images in elastography, however, the final pathological diagnosis were calcification or fibrosis in the lymph nodes. Thus, false positive does exist in our study. On the other hand, necrosis, hemorrhage or liquefaction in the malignant lesion could also cause false negative. Therefore, the accuracy of the EBUS-elastography score may be affected by the structure of the lymph nodes. In addition, EBUS-elastography is a subjective method and is largely related to the operator and the physiological situation (heart rate and respiratory rate) of the patient (Sigrist et al. 2017).

ROSE could evaluate the sample during the EBUS-TBNA. Although some studies indicated that no significant difference was identified in diagnostic value of EBUS-TBNA with or without ROSE (Sehgal et al. 2018). ROSE could provide rapid feedback for the sufficiency of the sample and therefore increase efficiency of the aspiration. ROSE could guide the operator for identifying the sampling site, determining the sufficiency of the sample and decreasing the procedure during (Sehgal et al. 2020). Meena et al. showed that pulmonologists with cytopathology training could perform onsite cytological evaluation of EBUS-TBNA samples, and no significant difference in accuracy of the sample was identified when compared with cytopathologists (Meena et al. 2016; Umeda et al. 2019), benefiting the clinical practice. In our study, ROSE was performed by a well trained pulmonologist. Our study showed that the sensitivity and specificity of ROSE in diagnosing malignant lymph nodes were 96.32% and 79.05% respectively, consistent with previous studies of 88.5% and 83.0%(Umeda et al. 2019)

In previous studies, ROSE was only applied as an ancillary study to evaluate the sufficiency of the sampling in EBUS-TNBA(Huang et al. 2017) (Gu et al. 2017). To better analyze the effects of elastography or ROSE, we combined elastography and ROSE for statistical analysis. Our results showed that the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of elastography and ROSE in diagnosing malignant lymph nodes were 86.61%, 92.65%, 11.78, and 0.14, respectively, and the AUC was 0.942, which was higher than those of the elastography alone or ROSE alone group. Since EBUS elastography or ROSE during EBUS-TNBA has been applied in multiple institutions, we believe that performing EBUS-elastography and ROSE together during EBUS-TNBA could improve the diagnostic capability.

Our study had some limitations. First, our study was a single institution study with limited sample sizes. Further study needs to be performed with a larger population. Second, our study only compared the value of the elastography score and ROSE, without additional information regarding lymph nodes' size, integrity and vascularity. Combining these factors may increase the diagnostic value of elastography and ROSE.

Conclusion

The combination of elastography and ROSE during EBUS-TBNA for patients with enlarged mediastinal lymph nodes, could increase the clinical diagnostic value compared with ROSE or elastography alone. We suggest the combination of elastography and ROSE during EBUS-TBNA in clinical practice.

Declarations

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Conflicts of interest : The authors have no conflict of interest to declare.

Ethics approval : This study was approved by the Ethics Committee of ZhongDa Hospital, School of Medicine, Southeast University.

Consent to participate: Informed consent was obtained from all patients.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

Figure 1

Representative lymph nodes status by EBUS elastography image analysis. a. Type 1, Predominantly non-blue (green, yellow, or red); b. Type 2, Partially blue, partially non-blue (green, yellow, or red); c. Type 3, Predominantly blue.

Figure 2

Representative lymph nodes status of Type 1 and 3 EBUS elastography image from 2 patients. a. 11R lymph node from patient with inflammation ; b.7# lymph node from patient with small cell carcinoma

Figure 3

Comparison of ROC curves of EBUS elastography, ROSE and combined EBUS elastography and ROSE groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table.xlsx](#)