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Letter to the Editor

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Reply to Letter to the Editor: "Influential Factors for Assessing Endobronchial Ultrasound Elastography" by Uchimura et al. Respiration. DOI: 10.1159/000510643

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Dear colleagues,

Thank you for your interest in our work on EBUS strain elastography [1] and for sharing your experience. In our reply, we will discuss the points raised and address several points for clinical application of EBUS strain elastography and for further research with this technology.

A first concern that is raised by the letter's authors is that patient characteristics or background exposure were not sufficiently described in our study to allow for complete evaluation of strain elastography performance [2]. Uchimura et al. [2] deem extensive background exposure information to be of significant influence for interpreting our EBUS strain elastography study results. We however would like to emphasize that our multicenter international study was specifically designed and aimed to prospectively evaluate the diagnostic value of EBUS strain elastography for predicting disease presence in individual lymph nodes of patients with lung cancer. As such, all patients with clinical pathology outcomes other than lung cancer were excluded from this analysis. The sole focus of our study was on EBUS procedures for a lung cancer diagnostic or staging purpose following the current international guidelines. Each patient had primary lung cancer visible on chest CT and/or PET scanning and either enlarged or FDG-PET avid lymph nodes, and centrally located tumors or suspicion of N1 disease. All relevant clinical information can be read in the CONSORT flow diagram (Fig. 1) which summarized all the excluded patients and shows that we explicitly focus on lung cancer [1].

The authors question if tuberculosis and pneumoconiosis exposure might have affected our study outcomes. However, both are very rare in the countries where our study was performed. It is therefore not expected to have had an influence on our study results. Sarcoidosis however may be of more relevance in the differential diagnosis of lung cancer in our population. The results of EBUS strain elastography in sarcoidosis are studied in more detail in collaboration with Professor Trisolini's team and have been recently published [3, 4]. In that study, we present preliminary evidence that lymph node relative strain, as measured by EBUS strain elastography, is a likely surrogate of the extent of fibrosis and is significantly associated with increased inadequacy rate of EBUS-TBNA specimens in sarcoidosis [4].

With these findings, we agree with the authors that comorbidity or secondary exposure of patient populations might influence study results and require additional in-

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vestigation. This is also a reason why we report in the discussion section of our study that not only ultrasound system but also demographic differences between centers/populations requires individual centers to again evaluate their own strain elastography performance before integrating it in their local clinical routine. There is indeed good possibility that different pathologies – as can be also expected from classical tactile palpation experience – increase lymph nodal stiffness.

In their letter to the editor, Uchimura et al. [2] report using a strain ratio for providing evidence that pneumoconiosis and other environmental exposures may relevantly increase nodal stiffness, an interesting fact which possibly should be studied further in a prospective trial. We would however again like to stress the importance of standardization if using strain elastography for reporting on pathology. While the authors report a strain ratio that could be of potential value, we would like to refer to our prior publication [5] and its online supplement where we show the strain ratio is a less reliable methodology. Based on our results we would ask to replace the strain ratio by the mean strain (histogram) method in future studies, where the mean strain of the lymph node region is related to the complete remainder of the image. The strain ratio is a measurement technique subjective to additional interpretation variability since alongside the lymph node of interest also a reference region of interest needs to be selected.

Another aspect that the authors question is the data depicted in Figure 3 of our study [1], in which we show lymph nodes to have a 73% probability of being malignant when they are >8 mm size, are FDG avid, and have a mean strain <115. The authors question if false positive findings might be explained by secondary exposure to either tuberculosis or occupational dust as these showed lower lymph node strain ratios in their studies. This is an interesting suggestion, and we cannot exclude the possibility that this occasionally could have been involved. However, we question if this is the main cause of false positive results. Again, as we were focused on obtaining the highest sensitivity and negative predictive value as possible in determining our cut-off, it is almost self-explanatory that false positives were included but considered of lesser importance. We additionally question why the authors think these exposures would be more significant than smoking, a frequent factor in lung cancer patients. Further studies elucidating the importance of these factors would however be valuable and still need to be performed.

Last, we would like to again stress that we think EBUS strain elastography is not a standalone diagnostic test. This technology will only depict relative stiffness of the target lymph node in relation to the surrounding tissue. This is obtained by measurements in the axial direction, upon minute compressions from the beating heart and large vessels. Our study shows that in a large multicenter study in patients with lung cancer, EBUS strain elastography is able to help determine the risk of malignancy in mediastinal and hilar lymph nodes in combination with size as well as with FDG-PET. The combined use is most accurate and should be used. This may help the endoscopist to select the most suspected lymph nodes for aspiration, which is essential for adequate staging. We fully agree that further research should be performed to assess if it is also of added clinical value in other pathology.

Conflict of Interest Statement

No conflicts of interest in relation to this letter. COI statements are enclosed in the original manuscript (reference [1]).

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Author Contributions

All authors contributed equally and have approved this reply letter.

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