Role of shear-wave and strain elastography to differentiate malignant vs benign subpleural lung lesions

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1. Introduction

For years, the lung has always been considered an organ that cannot be examined by ultrasound due to its air content (>90%). The lung has always been considered an organ that cannot be examined by ultrasound due to its air content (>90%). However, recent studies have shown that ultrasound can be used to diagnose lung lesions in certain conditions [1-3]. The application of lung ultrasound has extended from the field of hepatology to the field of thoracic imaging [4-5].

Elastosonography is a non-invasive diagnostic method to evaluate tissue stiffness. The aim of our study was to demonstrate the applicability and efficacy of elastosonography to differentiate benign vs malignant subpleural lung lesions compared to clinical, radiological, and histological findings.

We performed both strain and shear wave velocity (SWV) elastosonography on subpleural lung lesions. Moreover, we elaborated a composite score called “elasto index.”

Fourteen patients, 10 males and 4 females were recruited. On strain elastography, 9 lesions showed a hard pattern (type 3), 3 lesions showed an intermediate pattern (type 2), and 2 lesions a soft pattern (type 1). All lesions showed a mean SWV value of 4.46 ± 2.37 m/second. The mean SWV for malignant lesions (n = 6) was 5.92 ± 2.8 m/second. The mean SWV for benign lesions (n = 8) was 3.36 ± 1.20 m/second. SWV shows an area under the curve (AUC) of 0.792, and the Youden index shows a value of 3.6 m/second. The ROC curve elaborated for the diagnosis of malignancy by strain elastography showed an AUC of 0.688. ROC curve for the diagnosis of malignancy by elasto index demonstrated an AUC of 0.802. SWV values obtained by ARFI elastosonographic method are higher in malignant lung lesions (mean SWV: 5.92 m/second) than in benign ones (mean SWV: 3.36); a composite score (elasto index) is characterized by better statistical significance for the differentiation of the lesions.

Abbreviations: ARFI = Acoustic Radiation Force Impulse, AUC = area under the curve, CT = computed tomography, IQR = interquartile range, MR = magnetic resonance, PET = positron emission tomography, ROI = region of interest, SWV = shear-wave velocity, TE = transient elastography.

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displacement, which can be detected by the probe. Few published studies have experimented with the application of elastasonography in pulmonary diseases.\textsuperscript{6,7}

The main aim of our study is to demonstrate the applicability and efficacy of elastasonographic measurements in differentiating benign vs malignant subpleural lung lesions (benign lesions such as pneumonia vs malignant cancer lesion) compared to clinical, radiological (CT/PET) and histological findings.

2. Material and methods

2.1. Study patients

We recruited patients displaying clinical, radiological and histological diagnosis of subpleural lung lesions, admitted on the Pneumology and Internal Medicine wards. Ultrasound examination were performed in Internal Medicine ultrasound unit. Patients with subpleural lung lesions of size < 1 cm and those with pleural effusion were excluded. It was not possible to recruit a healthy control group due to the non-applicability of elastasonography to normally ventilated and non-pathological lung. After giving written and informed consent, 14 subjects (10 males), with a mean age of 67 (18–87) years, were enrolled in the study. The clinical characteristics of the study subjects are summarized in Table 1.

This work is the result of a retrospective analysis on data obtained during normal clinical practice from lung ultrasound scans performed between January 2018 and December 2019, in which elastasonography was used as a diagnostic completion, subject to the acquisition of informed consent from each patient. Therefore, no IRB approval is available for this work. From those preliminary observations, a prospective observational study protocol has been designed and is in the process of being approved by the relevant ethics committee.

2.2. Methods

The ultrasound examinations and elastasonography were performed by the same sonographer, who had at least 2 years of experience in the method. The ultrasound and elastasonographic examinations were performed with a convex probe, for the shear-wave method, and linear probe, for the strain method, with the EPIQ Philips device.

Shear waves are generated by ultrasound pulses of a given acoustic radiation strength. The velocity of the shear wave is then estimated by a Doppler effect on a region of interest (ROI) and is related to the stiffness or elasticity of the medium. This shear wave velocity can be used to calculate the tissue stiffness by the formula $E=\rho v^2$, where $E$ is the elasticity of the tissue (Young modulus, kPa), $\rho$ is the density of the tissue (kg/m$^3$) etc. is the speed of the shear wave (m/second).

 During the B-mode ultrasound examination, patients were on supine position on normal breathing. After B-Mode ultrasound examination, the quantification of the shear wave velocity (SWV) was performed by placing the probe on intercostal scan, to avoid the mechanical effort given by the presence of the ribs. The transducer was placed in contact with the skin slightly to minimize operator-dependent pressure on the chest. An acoustic radiation force impulse (ARFI) technique was used combined with virtual tissue imaging software (Philips EPIQ). During SWV measurement, the patient was asked to hold his breath and not to cough, strain or move. SWV quantification was performed on the axial plane obtained from central area of the lesion. The region of interest (ROI) was located on the solid and well visualized sections of the lesions, avoiding the necrotic and/or cystic areas (Fig. 1). SWV within the ROI has been automatically quantified in meters per second (m/second). Measurements were repeated for 3 consecutive times. SWV means for each lesion were measured and then compared with clinical, radiological and histological data. Subsequently, we elaborated a subdivision into 4 groups based on the results of SWV analysis:

- Group I: 1–3 m/second;
- Group II: 3–6 m/second;
- Group III: 6–9 m/second;
- Group IV: >9 m/second.

In relation to strain technique, the color box was located in the solid and well-visualized sections of the lesions; the qualitative

| Table 1 | Clinical findings of study patients. |
|---------|-------------------------------------|
| Variable | Value |
| n | 14 |
| Age, years | 67 (18–87) |
| Male sex, n (%) | 10 (71.4) |
| Hypertension, n (%) | 5 (35.7) |
| Atrial fibrillation, n (%) | 1 (7.1) |
| Pulmonary hypertension, n (%) | 2 (14.2) |
| Type 2 diabetes, n (%) | 2 (14.2) |
| COPD, n (%) | 4 (28.5) |
| IPF, n (%) | 1 (7.1) |
| ACE-I, n (%) | 0 (0) |
| ARB, n (%) | 2 (14.2) |
| Diuretics, n (%) | 3 (21.4) |
| Beta-blockers, n (%) | 1 (7.1) |
| DOAC, n (%) | 0 (0) |
| Warfarin, n (%) | 1 (7.1) |
| PPI, n (%) | 4 (28.5) |

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; PF, idiopathic pulmonary fibrosis; DOAC, direct oral anticoagulant; PPI, proton pump inhibitors.

Figure 1. SWV quantification was performed on the axial plane obtained from central area of the lesion. The region of interest (ROI) was located on the solid and well-visualized sections of the lesions, avoiding the necrotic and/or cystic areas. SWV has been automatically quantified in meters per second (m/second). The lung lesion is highlighted by the red dotted line.
study, based on the color scale encoding the blue color as hard and red as soft, led to the classification of the lesions based on the homogeneity and percentage of presence of the red signal (Type I: blue color <25% - soft lesion; Type II: blue color 25% to 75% - intermediate lesion; type III: blue color >75% hard lesion) (Fig. 2).

Eventually, in order to elaborate a score accounting both the SWV (quantitative) and the strain (qualitative) methods, we elaborated an “elasto index”: elasto strain value + SVW group value (Minimum value 2 - maximum value 7). This score was compared with the definitive histological diagnosis of the lesions.

3. Statistical analysis

Univariate associations were evaluated by the Spearman rank correlation test. Data are presented as median interquartile range (IQR). P values <.05 were considered statistically significant. Furthermore, ROC curves have been elaborated for the calculation of the AUC, of the sensitivity and specificity of the elastosonographic values. All tests were two-sided and analyzes were performed using the SPSS statistical package (see 16.0, APSS, Chicago, IL, USA).

4. Results

Fourteen patients, 10 males and 4 females were recruited. The mean age was 67 years. The baseline characteristics of the patients are listed in Table 1. It was possible to detect the lesions reported to the radiological examinations (chest CT) in all examined cases (see Table 2). The mean size of the lesions was 4.1 cm. On strain elastography analysis, 9 lesions showed a hard

![Figure 2. B-mode and strain elastosonography of sub-pleural lung consolidation; the lesion displayed a blue pattern >75% (hard lesion). The lung lesion is highlighted by the red dotted line.](image)

Table 2

Comparison between different features of the examined lung lesions.

| SEX | Strain Pattern | Stiffness (kPa) | Malignancy CT Features | Histological Features                  | Color-Doppler Flow |
|-----|---------------|----------------|------------------------|----------------------------------------|-------------------|
| M   | 3             | 10.5           | L                      | Choriocarcinoma metastasis             | +                 |
| F   | 1             | 3.4            | UD                     | Small cell lung cancer                 | 0                 |
| M   | 3             | 4.6            | L                      | Adenocarcinoma                         | 0                 |
| M   | 3             | 4.5            | UD                     | Adenocarcinoma                         | +                 |
| M   | 2             | 3.9            | U                      | Pneumonia                              | 0                 |
| F   | 2             | 5.1            | UD                     | Pneumonia                              | 0                 |
| M   | 3             | 2.8            | U                      | Micotic pneumonia                      | 0                 |
| M   | 3             | 3.8            | UD                     | Small cell lung cancer                 | 0                 |
| F   | 1             | 1.7            | U                      | Pneumonia                              | 0                 |
| F   | 3             | 3.6            | U                      | Ab ingestis pneumonia                  | 0                 |
| M   | 1             | 2.0            | U                      | Pneumonia                              | 0                 |
| M   | 3             | 3.0            | U                      | Pneumonia                              | 0                 |
| M   | 3             | 4.9            | L                      | Squamous cell carcinoma                | 0                 |
| M   | 3             | 8.3            | L                      | Squamous cell carcinoma                | +                 |

Malignancy CT features are reported as: likely, L; unlikely, U; undetermined, UD.
pattern (type 3), 3 lesions showed an intermediate pattern (type 2), and 2 lesions a soft pattern (type 1). The elastosonography performed on all lesions showed a mean SWV value of 4.46 ± 2.37 m/second. The mean SWV value for malignant lesions (n = 6) was 5.92 ± 2.8 m/second. The mean SWV value for benign lesions (n = 8) was 3.36 ± 1.20 m/second (Fig. 3). On statistical analysis, SWV values did not significantly correlate with age (P = .259; Rho = -0.324) and lesion size (P = .350; Rho = 0.270) (Fig. 4). If a ROC curve is elaborated for the malignancy diagnosis, SWV shows an area under the curve (AUC) of 0.792, and the calculation of the Youden index shows a value of 3.6 m/second. Regarding the strain elastography analysis, it did not show statistically significant correlations with age (P = .628; Rho = 0.142), and size of lesions (P = .686; Rho = 0.119). The ROC curve elaborated for the diagnosis of malignancy by strain elastography showed an AUC of 0.688, and the calculation of the Youden index showed a value of 2.5. Elasto index did not correlate with patient age and size of lesions. ROC curve elaborated for the diagnosis of malignancy by elasto index demonstrated an AUC of 0.802, and the calculation of the Youden index showed a value of 4 (Figs. 5 and 6) (Table 3).

5. Discussion

The first data to report is that all lung lesions reported on the chest CT as subpleural have been evidenced by B-mode ultrasound. For years, lung ultrasound was not considered “feasible” due to the physical properties of the lung tissue due to high difference in acoustic impedance between the tissues. Moreover, the main limitation of lung ultrasound is that the consolidation should involve the peripheral portion of the lung and “touch” the pleural line, thus changing the physiological A
line pattern created by the normal air/chest wall tissues interface. Furthermore, although we can estimate the lesion size on ultrasound, it almost never corresponds to the real 1, as the margins are often blurred and the limit in depth is almost never clear.

By B-mode ultrasound, lung atelectasis, inflammatory consolidations, tumors masses, pulmonary infarcts all appear with a substantially gray scale echostructure, as like to the sonographic feature of the liver, from which the term “hepatization” of lung tissue. Indeed, several studies and authors have attempted to create a differential semiotics of the various lesions, based on the presence of signs such as shape, margins, echostructure, evidence of vascularization, the presence of air and fluid bronchograms.

However, no specific sign has been shown to be able to differentiate malignant lesions from benign ones with absolute specificity. Particularly, air bronchograms are present both in tumor lesions and in pneumonia consolidations. Furthermore, the color-Doppler examination is possible in some lesions only, and it is not suggestive for the nature of the lesion (in our sample 3 the color-Doppler examination is possible in some lesions only, tumor lesions and in pneumonia consolidations. Furthermore, our data seem to agree with previous works showing higher metastatic lesions. In contrast, Ozgokce et al demonstrated that the mean SWV (4.12 m/second) of metastatic lesions was higher than primary lung cancers (3.43 m/second).

In our opinion, current data on elastosonography to study subpleural lung lesions are almost “primordial”. Indeed, the number of patients examined is small in different studies, and the methods of study are often not comparable; elastosonographic methods (ARFI vs TE), the probes and, finally, dedicated machines and softwares are different. Moreover, in some cases the final diagnosis of the nature of the lesion was not supported by histological data. The main limitation of the method seems to be due to the peculiarity of the lung tissue; a large proportion of non-peripheral lesions cannot be examined by ultrasound; secondly, it is not possible to perform an ultrasound study of lesion margins, although some data showed an excellent specificity in the study of parietal infiltration of lesions.

Similar to our data, in the study by Sperandeo et al patients age and the size of the masses (3.06 ± 0.88 cm) were not significantly associated with histopathological types. A further study by Lim et al found that the velocity rate of deformation of primary lung tumors was higher than metastatic lesions. In contrast, our data and colleagues demonstrated that the mean SWV (4.12 m/second) of metastatic lesions was higher than primary lung cancers (3.43 m/second).

In our case, the highest SWV value was obtained on a metastatic choriocarcinoma lesion, with values of 10.58 m/second (Fig. 7).

We also believe that the SW method can be useful in determining the area to be biopsied in the widest subpleural lung lesions, with heterogeneous and necrotic areas. In our study 2 lesions clearly showed a necrotic core. Therefore, the accuracy in selecting the “target” point in biopsy procedures could be increased, thus improving the safety profile of the procedure.

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### Table 3

| Feature   | Area  | STD error | Asintotic sign | IC 95% (low) | IC 95% (max) |
|-----------|-------|-----------|----------------|--------------|--------------|
| SWV       | 0.792 | 0.122     | 0.071          | 0.553        | 1.00         |
| STRAIN    | 0.688 | 0.144     | 0.245          | 0.405        | 0.97         |
| Elasto index | 0.802 | 0.127     | 0.051          | 0.554        | 1.00         |

Shear wave velocity, SWV.
Given the lack of uniformity, there is currently no threshold value or classification, as for the Metavir scale for hepatic stiffness in hepatitis, which can classify and discriminate the nature of the lesions. We proposed both a scale of values regarding the evaluation of SWV and a strain classification to differentiate lesions; finally we elaborated an elasto index in order to merge the qualitative information of the strain and the quantitative information by the SWV, so to increase the diagnostic accuracy.

6. Limitations of the study
There are some limitations in our work. First, since we used a linear probe in some patients, the subcutaneous adipose tissue in some subjects may hinder the correct measurement of elastosono- graphic methods. The second limitation was that all patients had a subpleural CT lesion; it was not possible to examine the consolidations that did not reach the pleural line; furthermore, due to the peculiarity of the application of the method to the lung tissue, it was not possible to examine a control group or assess marginal differences between the stiffness of the pathological tissue and that normally ventilated. A further limitation is that our study included a limited number of cases.

7. Conclusions
Our study demonstrates that SWV values obtained by ARFI elastosonographic method are higher in malignant lung lesions than in benign ones; when the numerical data of the SWV is combined with the qualitative data of the strain elastography thus obtaining a composite score, a good statistical significance is reached for the differentiation of lung lesions. Therefore, the present study may reinforce the preliminary data on the application of transthoracic elastosonography in evaluating subpleural lung lesions. Transthoracic elastosonography can be a non-invasive, repeatable method, without contraindications, executable even at bed-side, to evaluate subpleural lesions. In the future, multicenter studies will be required, performed on a large sample of subjects, with uniformity of methods, which may lead to more definitive conclusions regarding the application of elastosonography to the lung field, and the possible creation of a scale or cut-off values.

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