RESEARCH ARTICLE

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Shear Wave Ultrasound Elastography and Diffusion-Weighted Magnetic Resonance Imaging Findings of Pleural Based Masses with Histopathologic Correlation

ABSTRACT

Objective: The study aims to evaluate the usefulness of non-invasive diagnostic methods, shear wave elastography (SWE), and diffusion-weighted magnetic resonance imaging (DWI) to differentiate benign and malignant lesions in the thoracic pleural based masses by comparing them with histopathological findings.

Methods: Sixty-three patients having a pleural-based peripheral mass on computed tomography (CT), admitted to the interventional radiology department for transthoracic biopsy, were included in the study. All patients underwent DWI, and ADC values of the groups were measured. Transthoracic biopsy was performed with the guidance of US from the area where the highest shear wave velocity (SWV) value was calculated. ADC and SWV values of histopathologically proven benign and malignant lesions were statistically compared.

Results: Fifty-six patients were male, and seven were female. The mean age was 64.68±10.13 years (41-85 years). Fourty-four patients were malignant, and 19 were benign. The maximum SWV was found to be 4.13±0.59 m/s in malignant cases and 3.55±0.71 m/s in benign cases, and the difference was significant (p = 0.001). Mean ADC value was measured as 1.04±0.30 x 10-3 mm2/s in malignant cases and 1.32±0.33 x 10-3 mm2/s in benign cases on DWI and the difference was significant (p = 0.002). In malignant cases, the minimum ADC was 0.73±0.29 x 10-3 mm2/s, and 0.99±0.44 x 10-3 mm2/s in benign cases, the difference was significant (p = 0.024). ROC analysis revealed a cut-off value of ≥4.08 m/s for SWVmax, ≤1.01x10-3 mm2/s for mean ADC, and ≤0.8x10-3 mm2/s for minimum ADC showed a significant performance in distinguishing malignant and benign lesions.

Conclusions: Transthoracic US elastography and DWI are useful in differentiating malignant and benign lesions in appropriate cases. Both SWE and DWI are useful in routine use because they are non-invasive and do not contain radiation. In particular, SWE is suitable for biopsy guidance and may prevent the possibility of insufficient material.

Keywords: Shear Wave Elastography, Diffusion-Weighted MRI, Biopsy, Mass, Thorax.

Plevra Tabanlı Kitlelerde Shear Wave Elastografi Ve Difüzyon MRG Bulgularının Histopatolojik Bulgular İle Korelasyonu

ÖZET

Amaç: Non-invaziv tanısal yöntemler olan shear wave elastografi (SWE) ve difüzyon ağırlıklı magnetik rezonans görüntülemenin (DAG), toraksta plevra tabanlı kitlelerde benign ve malign lezyonların ayırımında kullanılabilirliklerinin histopatolojik bulgular ile karşılaştırılarak değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Mart 2015 ile Mart 2018 tarihleri arasında girişimsel radyoloji ünitesine transtorasik biyopsi amacıyla başvuran, bilgisayarlı tomografide (BT) plevra tabanlı kitle izlenen ve biyopsiye uygun bulunan 63 olgu çalışmaya dahil edilmiştir. Tüm olgulara DAG yapılmış ve kitlelerin ADC değerleri ölçülmüştür. Tüm olgulara SWE uygulanmış ve en yüksek SW hızı ölçülen alandan transtorasik biyopsi yapılmıştır. Histopatolojik olarak benign ve malign olduğu belirlenen lezyonların DAG ve SWE bulguları karşılaştırılmıştır.

Bulgular: Olguların 56'sı erkek, 7'si kadındı. Ortalama yaş 64.68±10.13 idi (41-85). Olguların 44'ü malign, 19'u ise benigndi. Malign olgularda maksimum SW hızı ortalama 4.13±0.59 m/sn, benign olgularda ise 3.55±0.71 m/sn ölçülmüş olup fark anlamlı idi (p=0.001). Malign olgularda mean ADC 1.04±0.30 x 10-3 mm2/sn, benign olgularda ise 1.32±0.33 x 10-3 mm2/sn ölçülmüş olup fark anlamlı idi (p=0.002). Malign olgularda minimum ADC 0.73±0.29 x 10-3 mm2/sn; benign olgularda ise 0.99±0.44 x 10-3 mm2/sn ölçülmüş olup fark yine anlamlı idi (p=0.024). ROC analizi sonucu maksimum SW hızı değeri ≥ 4.08 m/sn, mean ADC değeri ≤1.01x10-3 mm2/sn ve minimum ADC değeri ≤ 0.8x10-3 mm2/sn malign tanısı için cut-off değeri olarak alındığında, başarılı şekilde malign-benign ayrımı yapılabilmekteydi.

Sonuç: Transtorasik US elastografi ve difüzyon MR, uygun olgularda malign-benign lezyon ayrımında yararlıdır. Hem SWE, hem de difüzyon MR incelemesi, radyasyon içermemeleri ve non-invaziv olmaları nedeniyle rutin kullanımda kullanışlı yöntemlerdir. Özellikle SWE, biyopsi kılavuzluğu için uygun olup yetersiz materyal olasılığını engelleyebilir.

Anahtar Kelimeler: Shear Wave Elastografi, Difüzyon MRG, Biyopsi, Kitle, Toraks.

INTRODUCTION

Ultrasound elastography can detect soft tissue elasticity and hardness and has been used more frequently in diagnosing thyroid, breast, prostate, and liver cancers and evaluating liver fibrosis in the recent decade (1-6). Diffusion MR imaging, although primarily used in neuroradiology, is an imaging method that can be applied to many parts of the body and is increasingly used in differentiating benign and malignant lesions. Its use in the thorax is also becoming widespread (7-10). Both methods are easy-to-apply, fairly rapid, non-invasive, and safe imaging methods used in research to distinguish malignant vs. benign lesions. Computed tomography (CT) is mostly used for the diagnosis of thoracic lesions due to the bone structure of the chest wall and the air content of the lungs, and tomography-guided biopsy may be taken from suspicious lesions. CT-guided biopsy is a valuable method and an accurate, safe and effective procedure when performed in an adapted environment (11,12). However, radiation is used in CT, albeit at a low dose. Besides, if the lesion is necrotic and/or close to vessels or cannot be distinguished from accompanying atelectasis, it may be necessary to use contrast material during biopsy in some cases (12). CT cannot provide information about tissue stiffness, viable tumor tissue may not be determined clearly in some cases, the biopsy material may not have sufficient diagnostic value, and the biopsy may have to be repeated. This study aims to find the area where the tumor cells in the tissue to be biopsied by applying SWE and diffusion MRI before transthoracic biopsy for definitive diagnosis of pleural-based (pleural or subpleural) masses, to reduce the possibility of insufficient material and to prevent the need for repetition of the biopsy. Also, by correlating the histopathological diagnosis (benign/malignant feature) of the biopsy material with elastography and diffusion MRI findings, it will be investigated whether the imaging methods will determine the nature of the tumor without the need for invasive procedures.

MATERIAL AND METHODS

The study was conducted prospectively between March 2015 and March 2018. The cases were selected among the patients who had a chest CT-detected pleural-based solid mass, suitable for biopsy, MR, and US imaging. A total of 155 subjects referred to the interventional radiology unit with a transthoracic biopsy request were evaluated and 63 suitable cases were included in the study.

The criteria for inclusion in the study are:

- Having a pleural-based solid mass in chest CT and applying to our hospital's interventional radiology unit with the indication of biopsy.
- No contraindications for MR examination (contraindications include metallic foreign body in the body that are not compatible with MRI, metallic operation material such as a pacemaker, mechanical heart valve, severe claustrophobia, pregnancy (can be done by consulting a gynecologist and obstetrician))
- Being able to cooperate with all examinations

The exclusion criteria are:

- Central localization of the lesion (without pleural surface extention)
- Pure cystic lesions
- Previous diagnosis and treatment of the mass
- Contraindications for MRI and biopsy
- Not being able to cooperate with an examination

Informed consent form from all patients and ethics committee approval were obtained.

Diffusion MRI was performed to the patients first. Then they were taken to US and the images were compared.

Diffusion-weighted imaging (DWI) was performed with a 1.5 T MRI device (Hitachi Echelon, Tokyo, Japan) using a body coil, without breath-holding.

It was performed using two b values (b0 and b1000) in the axial plane, with a slice thickness of 5-10 mm and a slice interval of 1 mm, depending on the size of the lesion.

ADC (Apparent Diffusion Coefficient) measurements were made at the workstation from the area showing the most diffusion restriction in each lesion, and ADCmean (mean or average ADC) and ADCmin (minimum ADC) values were obtained.

Ultrasound and SWE examinations were performed using a Siemens ACUSON S2000 device and 4-MHZ 4C1 convex probe. ARFI (Acoustic Radiation Force Impulse) method (Virtual TouchTM Quantification/VTQ, Siemens, Germany) was used as the SWE technique. Scanning was performed with minimal scanning pressure applied by the operator and the patients were asked to stop breathing to minimize motion. A standard ROI (region of interest) box was used for sampling. This ROI has a predefined size provided by the system (1x0.5 cm). Sampling was not made

from necrotic and cystic components. Sampling was done 3-10 times from solid parts, depending on the size of the lesion. The highest shear wave velocity value (SWVmax) was recorded. The biopsy was attempted to be taken from the places with the highest shear wave velocity values.

Skin cleansing was provided with povidone-iodine in patients who were found suitable for biopsy in ultrasonography. After applying prilocaine (0.1 ml/kg) as a local anesthetic agent to the skin, subcutaneous and intercostal area, tru-cut biopsy (several samples) was taken from the mass with an 18-gauge biopsy needle after waiting one minute. The removed tissue was sent to the Pathology Department Laboratory in 10% formol solution. The patients without complications were discharged after the general condition of the patient was followed, and the pneumothorax control was performed on the PA chest radiographs taken 2 hours later.

The slides having 4 um-tissue sections were routinely stained by H&E and by immunohistochemistry whenever needed. The reporting was based on the 2015 WHO classification of Lung, Pleura, Thymus and Heart tumors.

Two cases for whom SWE measurement could not be performed were excluded from the study. During the biopsy procedure, minimal pneumothorax developed in only one case, which did not require tube thoracotomy. No complications were developed in other patients. There was no case in which insufficient material was reported histopathologically.

Imaging results were compared with histopathological findings in terms of benign versus malignant diagnosis.

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Statistical Analysis: Normal distribution prerequisite for continuous variables was examined with Shapiro-Wilk test and group comparisons were made with Independent Samples t-test. Relationships between categorical variables were examined with Pearson's chi-square or Fisher's exact test. ROC curve analysis was performed to determine cut-offs for parameters found to be significant. Statistical analyzes were made with the SPSS v.22 package program and the level of significance was taken into account as 0.05.

RESULTS

A total of 63 cases were included in the study. Fifty-six of the cases were male and seven were female. The mean age was 64.68 ± 10.13 (41-85). Forty-four of the cases were malignant, and 19 were benign. Of the malignant cases, 40 (90.9%) were male, 4 (9.1%) were female, and the mean age was 64.80 ± 10.41; of the benign cases, 16 (84.2%) were male, 3 (15.8%) were female, and the mean age was 64.42 ± 9.72. The demographic characteristics of the cases are shown in Table 1.

Table 1. The demographic characteristics of the cases

	Benign (n=19)	**Malignant (n=44)**	**p**	**Total(n=63)**
Age	64.42±9.72	64.80±10.41	0.894	64.68±10.13
Gender				
Male	16 (%84.2)	40 (%90.9)	0.422	56 (%88.9)
Female	3 (%15.8)	4 (%9.1)		7 (%11.1)
Smoking				
No	4 (%21.1)	4 (%9.1)	0.229	8 (%12.7)
Yes	15 (%78.9)	40 (%90.9)		55 (%87.3)

There were 44 malignant (32 non-small cell lung carcinoma (NSCLC), 4 small cell carcinoma (SCLC), 2 metastatic adenocarcinoma, 1 sarcomatoid carcinoma, 1 large cell neuroendocrine carcinoma, 1 malignant mesothelioma, 1 diffuse large B-cell lymphoma, 1 Hodgkin lymphoma, 1 malignant mesenchymal tumor) and 19 benign lesions (12 chronic inflammatory lesions, 4 acute inflammation/pneumonia, 1 tuberculosis, 1 solitary fibrous tumor, 1 thymoma).

Images of case samples are shown in Figure 1 and 2. The highest SWV (SWVmax) obtained from the measurements made from the lesions, ADCmin and ADCmean values calculated in DWI, the widest dimensions (measured on CT), and localization of the lesions (right-left lung) are shown in Table 2. Accordingly, a statistically significant difference was found between SWVmax, ADCmin, ADCmean, and size and malignant-benign characteristics of the lesion ($p < 0.05$).

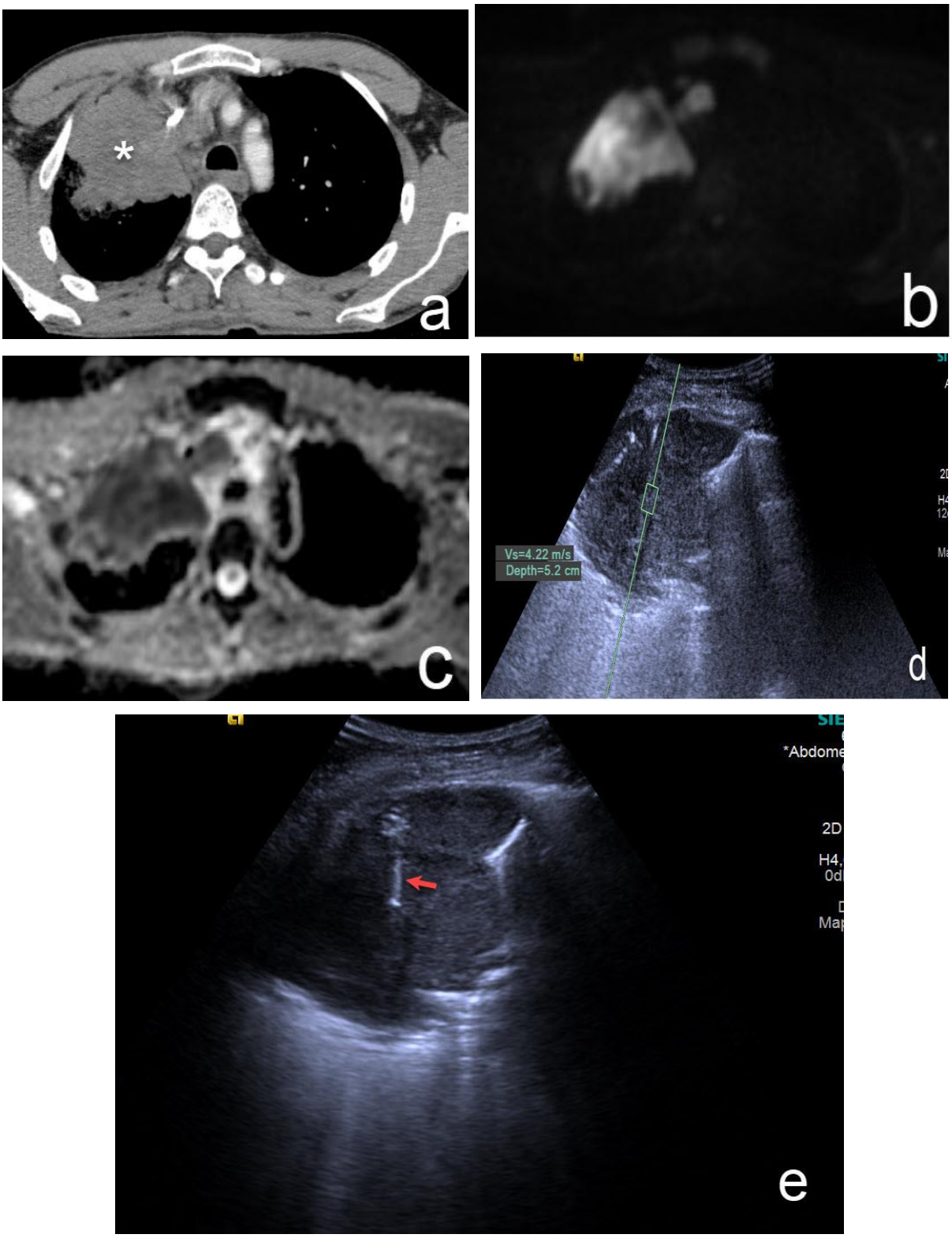

Figure 1. A 54-year-old smoker male with malignant right upper lobe mass (NSCLC). a. Axial CT image of the mass (asterisk). Axial DWI (b) and ADC map (c) show restricted diffusion. The mean ADC was 0.7x10-3 mm2/s and minimum ADC was 0.46x10-3 mm2/s. The maximum SWV value of the mass is 4.22 m/s (d) and the biopsy needle (e, arrow) is shown.

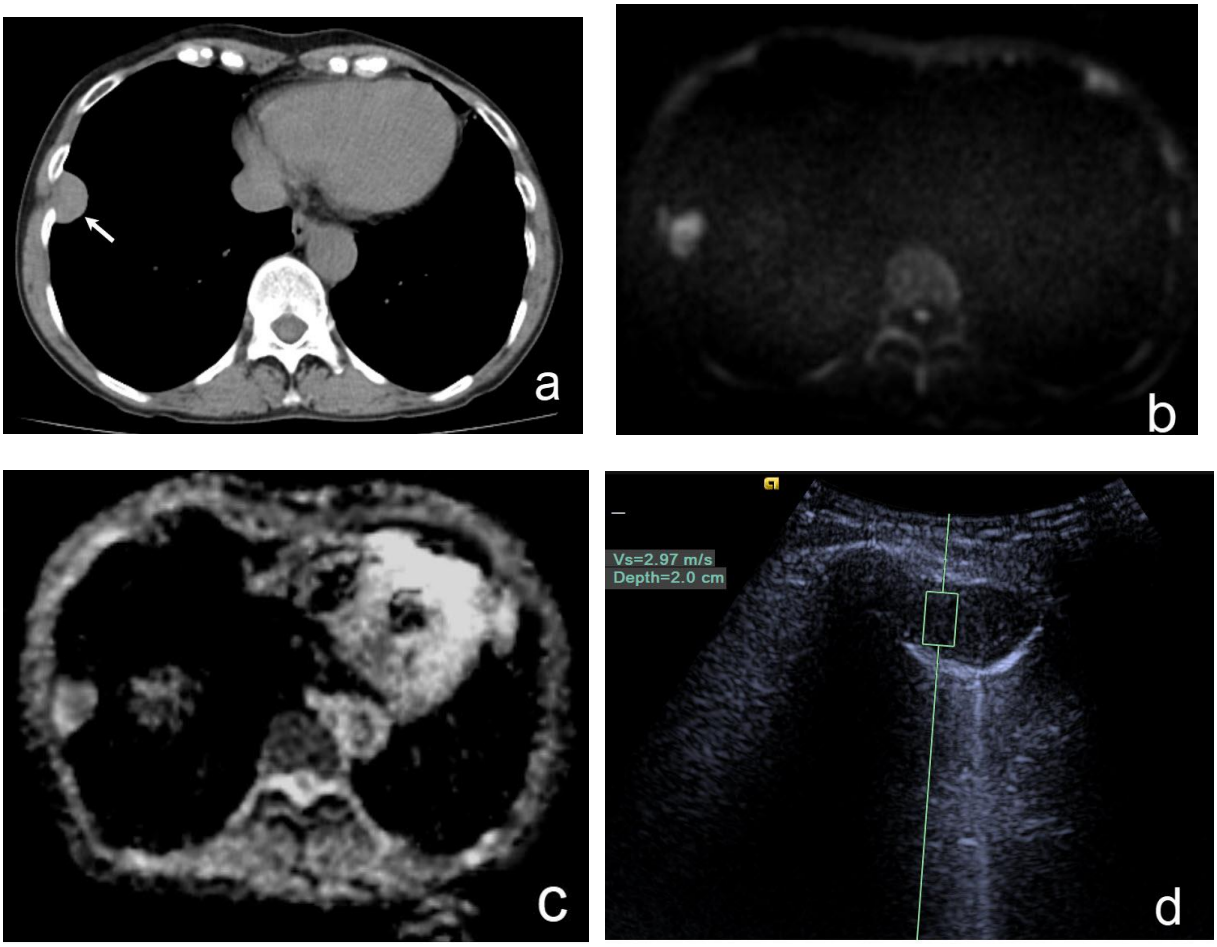

Figure 2. A 62-year-old smoker female with benign right pleural-based mass (solitary fibrous tumor). a. Axial CT image of the mass (arrow). Axial DWI (b) and ADC map (c). The mean ADC was $1.115x10^{-3}$ mm^2/s and minimum ADC was $0.3x10^{-3}$ mm^2/s. The maximum SWV value is 2.97 m/s (d).

Table.2. The SWV values, ADC values, size and sides of the lesions

	Benign (n=19)	**Malignant (n=44)**	**p**	**Total (n=63)**
SWVmax	3.55±0.71	4.13±0.59	***0.001***	3.95±0.68
ADCmin	0.99±0.44	0.73±0.29	***0.024***	0.81±0.35
ADCmean	1.32±0.33	1.04±0.30	***0.002***	1.13±0.33
Size	4.47±1.94	6.31±2.48	***0.006***	5.75±2.46
Side				
Right	13 (%68.4)	24 (%54.5)	0.305	37 (%58.7)
Left	6 (%31.6)	20 (%45.5)		26 (%40.0)

ROC analysis revealed that ADCmin cut-off value ≤$0.8x10^{-3}$ mm^2 / s (AUC = 68.1%; 95% CI = 51.6% to 84.7%; p = 0.023) to be a potential marker of malignancy with a sensitivity of 65.9% and specificity of 73.7%. The cut-off value of ≤$1.01x10^{-3}$ mm^2 / s for the ADCmean generated the combination of 61.4% sensitivity and 79% specificity in distinguishing malignant and benign cases (AUC=%73,6; 95% CI: 59,9% to 87,2%; p=0,003). And when the SWVmax value of ≥4.08 m / s is taken as the cut-off value for malignant diagnosis, it makes a successful distinction with 68.2% sensitivity and 84.2% specificity (AUC = 76.5%; 95% CI = 63.8% to 89.2; p = 0.001).

The ROC analysis results for benign vs. malignant lesion distinction are shown in Table 3.

Table.3. The ROC analysis results

	AUC	95% CI	p	Cut-off	Sensitivity	Specificity
SWV max	0.765	0.638 – 0.892	**0.001**	≥4.08	68.2	84.2
ADC min	0.681	0.516 – 0.847	**0.023**	≤0.80	65.9	73.7
ADC mean	0.736	0.599 – 0.872	**0.003**	≤1.01	61.4	79.0

DISCUSSION

Ultrasound elastography is a noninvasive imaging method that provides information about tissue stiffness and elasticity, has been increasingly used in recent years. When an external force is applied to a tissue, the tissue is deformed. The ability of the tissue to reach its original shape and size when the external force disappears is called elasticity. Tissue deformation is inversely proportional to the stiffness of the tissue. There are two basic elastography techniques: strain elastography and shear wave elastography. SE measures tissue stiffness by applying external tissue pressure by using probe pressure or through endogenous mechanical force (e.g. carotid pulsation). It is operator-dependent and may lead to inter-observer differences and can not give quantitative information. In shear-wave based elastography, a tissue shear-wave is induced by the imaging system. Measurement of shear wave velocity, tissue flexibility is evaluated qualitatively and quantitatively. In this mode, a short duration (0.3-0.4 ms), high power (frequency 2.67 MHz) acoustic radiation force impulse (ARFI) is applied to the tissue with US probes instead of external compression. Shear wave velocity is directly proportional to the hardness of the tissue (in m / s or kilopascals). In this technique, mild probe compression is sufficient, and user dependency is eliminated. However, if too much pressure is applied from the outside, there may be a false height in elasticity values (13,14). SWE was used in our study to eliminate user dependency and to obtain objective quantitative results.

Although ultrasonography in the chest is limited, it can be used for peripheral parenchymal, pleural, and chest wall diseases. Pleural thickening, pleural effusion, pneumothorax, pneumonia, or bronchopneumonia consolidations can be demonstrated by US (15,16). However, there is no specific US finding for the distinction between inflammation and malignancy in solid lesions. USE, on the other hand, has been a method that has been studied in the recent decade, as it provides information about tissue stiffness and malignant lesions are mostly harder than benign lesions (17-21). Sperandeo et al. (19) found that lung cancer is stiffer than pneumonia and concluded that USE could improve the accuracy and and yield of fine-needle aspiration biopsy as well as our study. Our results are similar to those of Sperandeo et al, but they used the compression elastography technique instead of SWE. Lim et al. (20) also found that the strain ratio of primary lung tumors was higher and stiffer than metastatic tumors. In the study of Ozgokce et al., it was emphasized that SWE is very useful in predicting malignancy in subpleural solid lesions, and it is a non-invasive method that can be used in the evaluation of subpleural lesions (21). The results of our study also support this study. In Ozgokce et al.'s study, not all cases were diagnosed histopathologically, and the findings were not evaluated together with diffusion MRI. In our study, all subjects were additionally visualized by DWI and confirmed histopathologically. Wei et al. assessed the diagnostic value of USE in differentiating between benign and malignant peripheral lung lesions by using conventional US, ARFI and point shear wave elastography (22). All cases were confirmed histopathologically. They concluded that USE helps to distinguish malignant lesions from benign lesions and ARFI elastography was more effective in diagnosing peripheral lung lesions. Our results are similar. Wei et al. reported the cut-off value of 1.951 m/s with a sensitivity of 70.9% and a specificity of 69.4% (22). Ozgokce et al. was found the cut-off value 2.47 m/s for the SWV value with sensitivity and specificity of 97.7% (21). When 4.08 m / s was selected as a cut-off value, a sensitivity of 68.2% and specificity of 84.2% were obtained in our study. We used the highest SWV value because we aimed to obtain a biopsy from the hardest part of the lesion. We used the highest SWV value because we aimed to obtain a biopsy from the hardest part of the lesion. Other studies have used the average-mean of multiple measurements from the lesions. The difference between the values is thought to be due to the difference in measurement techniques.

Although the use of MRI in the thorax is limited due to reasons such as respiratory and cardiac movements, vascular pulsations and sensitivity artifacts arising from the air-tissue interface, its use gradually increases. Due to the possibility of functional evaluation, DWI has begun to play an important role in the evaluation of tumoral diseases of the lung, mediastinum and lymph nodes (7,8). The density of the image in DAG increases or decreases with the diffusion ability of the molecules. Normal or increased diffusion, i.e. high ADC values, are seen in healthy tissues or benign pathologies. Diffusion restriction, i.e. low ADC values, indicates hypercellularity, cytotoxic edema, or dense content (hemorrhage or protein). Diffusion is restricted in malignant cells and low ADC values are observed. Because of this feature, DWI is also used in the differential diagnosis of malignant and benign diseases. Its clinical uses include evaluation of pulmonary nodules, characterization of lung tumors, differentiation of post obstructive pneumonia-tumor, evaluation of response after chemotherapy, evaluation of mediastinal lymph nodes and masses, and evaluation of pleural diseases (7,8, 23-25). A standard ROI (region of interest) measurement area or number has not been reported for ADC measurement from lesions. Besides, there is no full consensus on which ADCmin and ADCmean value should be used (9). In our study, both ADCmin and ADCmean were measured from each lesion. In the study of Luna et al. (23), DWI was reported to have

83% sensitivity and 74% specificity in distinguishing malignant lesions if the ADC value was accepted as $\leq 1.4x10^{-3}$ mm^2/s. In our study, when the ADCmin value $\leq 0.8x10^{-3}$ mm^2 / s is taken as the cut-off value for malignant diagnosis, it makes a successful distinction with 65.9% sensitivity and 73.7% specificity, and when the ADCmean value $\leq 1.01x10^{-3}$ mm^2 / s is taken as the cut-off value for malignant diagnosis, it makes a successful distinction with 61.4% sensitivity and 79% specificity.

Our study has some limitations. The masses could not be wholly visualized by ultrasonography (primarily due to the obstruction of the ribs) in all patients, diffusion images could not be fused with SWE and the biopsy needle could not be directed to the desired point in all cases.

CONCLUSION

Our study has shown that SWE and DWI are useful diagnostic methods for predicting malignancy in pleural-based masses. In particular, SWE is a suitable method for biopsy guidance. Since it is a non-invasive method that is easy to use, does not contain radiation and no need for contrast administration, it can be preferred to take the biopsy from the most suitable part of the lesion and can eliminate the possibility of insufficient/unsatisfactory material for histopathological evaluation as well.

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