Original Article

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Assessment of Stromal Elastin Fibers in Breast Cancer and Fibroadenomas: Is There a Correlation With Ultrasound Elastography Findings?

Nurşen Toprak[1], İbrahim Aras[2], Osman Toktaş[3], Adem Yokuş[1], Ali Mahir Gündüz[1]

[1]Department of Radiology, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey
[2]Department of Pathology, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey
[3]Department of General Surgery, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey

ABSTRACT

Objective: The stiffness of a breast lesion provides information on the likelihood of malignancy. The most important factor affecting this stiffness is the composition of the extracellular matrix (ECM). The aim of this study was to assess the elastin fiber contents of malignant breast lesions and fibroadenomas and investigate any relationship between the shear wave velocity (SWV) measured by ultrasonography, and the elastin fiber content of lesions.

Materials and Methods: Consecutive patients with breast lesions were enrolled. The SWV values of the lesions were analyzed. Histopathological analysis of elastin in excised lesions was performed by the method of Shivas and Douglas. Breast cancer patients were reviewed according to their lymph node status and tumor diameter. The relationship between SWV value and tissue elastin fiber score was analyzed. The correlation between breast cancer grade and elastin fiber score in malignant lesions was investigated.

Results: A total of 167 consecutive breast lesions in 167 patients were included in this study (75 invasive cancer, 92 fibroadenomas). High elastic fiber score was significantly more common (p = 0.001) in malignant lesions (n = 61; 81.3%) than fibroadenomas (n = 13; 14.1%). There was a negative correlation between the mean SWV and the elastin fiber score of fibroadenomas (p = 0.001). A low grade in breast cancer was associated with high elastin fiber score (p = 0.01).

Conclusion: Malignant lesions tend to have higher elastin fiber scores than fibroadenomas. Elastin fiber assessment may provide additional prognostic information in malignant lesions. Changes in elastin fiber content may account for the variation in elasticity in fibroadenomas.

Keywords: ARFI elastography; breast cancer; elastin fiber; fibroadenoma

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Key Points

- This study is a novel method for breast imaging that assesses the elasticity of a range of breast lesions.
- Although the effect of ECM components on breast lesion stiffness is important, there is little research on this subject.
- Elastin fiber is a protein that can change the stiffness of fibroadenomas. Therefore, it can be used to differentiate fibroadenomas from malignant lesions.
- Since the elastin fiber score is higher in low-grade breast cancers, it may have some use as a prognostic marker, if sufficient evidence is available.

Introduction

The extracellular matrix (ECM) is a complex network that is mainly comprised of interstitial collagen, elastin fibers, fibronectin, and many types of proteoglycans (1). An excessive accumulation of the components of the ECM is observed in breast carcinoma (2). This accumulation in invasive cancers causes stiffness of the tissue and thus promotes tumor invasion and metastasis (3).

Some studies have shown that collagen fibers, the main protein in ECM, may play an important role in the stiffness of breast lesions (4, 5). Elastin fiber is the second most important protein in the ECM and is responsible for the elasticity of the tissues. In a study investigating the relationship between ECM proteins and stromal stiffness, collagen fiber and elastin fiber were both associated with the stiffness of breast lesions (6). While earlier studies have investigated the relationship of collagen with tissue stiffness, there is no study investigating the role of elastin

Corresponding Author:
Nurşen Toprak; nursentoprak31@gmail.com

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in tissue stiffness (4, 5). Thus, the individual contribution of elastin fiber in the stiffness of breast lesions is still not entirely clear. Large aggregates of elastin fibers, a condition known as elastosis, are found in breast cancer stroma (1, 7, 8). Elastosis is usually associated with breast cancer, but it has also been reported to occur inconsistently in fibroadenoma (9).

In various breast pathologies, the most important radiological method to assess the stiffness or flexibility resulting from the differentiation of various proteoglycans in the ECM is ultrasound elastography (USE). In the literature, several studies have reported that shear wave elastography (SWE) showed good performance in assessing benign and malignant breast lesions. SWE is an objective and quantitative method for estimating tissue stiffness. Some studies have evaluated the correlation between SWE and ECM components in breast lesions (5, 6, 10, 11).

To the best of our knowledge, there is no study in the literature investigating the effect of elastin fiber content on stromal stiffness in, fibroadenomas and invasive breast cancer. The aim of this study was to investigate the relationship between elastin fiber content and the shear wave velocity (SWV), one of the parameters obtained from SWE, in fibroadenomas and breast cancer.

Materials and Methods

Patients

The study was conducted in the Breast Radiology Unit and Pathology Unit of the Van Yüzüncü Yıl University Faculty of Medicine from October 2018 to March 2019. The study was approved by our University Ethics Committee (decision number: 2020/03-09, date: 22/05/2020).

Retrospectively, patients with Breast Imaging Reporting and Data System (BI-RADS) 4-5 breast masses were included in the study. Patient consent was waived due to the retrospective nature of the study. An ultrasound (US)-guided, cutting needle biopsy was performed on all lesions, and histopathological results of the lesions were obtained. Patients with histopathological results diagnosing invasive breast cancer or fibroadenoma were included. Patients with breast lesions with other benign histopathology or diagnosed with ductal carcinoma *in situ* were excluded from the study.

Ultrasound and Shear Wave Elastography

US was performed by a radiologist with 10 years of experience in US and 5 years-experience with breast USE. Bandwidth linear array transducer probes of 14 MHz were used for US and 9 MHz probes for acoustic radiation force impulse (ARFI) elastography evaluation (Acuson-S2000; Siemens Medical Solutions, Mountain View, CA, USA).

Breast lesions detected by US, and following The American College of Radiology (ACR) BI-RADS criteria, were evaluated based on assessment of margin, shape, orientation, echo pattern, calcification, and posterior features (12).

In ARFI elastography, the virtual touch tissue quantification (VTTQ) option was used. During elastography, the parameters for the "breast" option were used with the "factory pre-set". A 5-mm-wide US probe at a frequency of 9 MHz was used to approach the lesion using gel. No pressure was applied to the skin. Split-screen display mode was used to obtain US and elastography images of the same location. When the lesion was visible on US, the patient was instructed to hold her breath, and elastography images were obtained. It is known that breast lesions show heterogeneous internal structure and in elastography images hard areas of the lesion appear white and soft areas black. The regions of interest (ROIs) on the VTTQ measuring 1 mm × 1 mm was used to provide related SWV values. Although the number of ROIs varies according to the lesion size, an equal number of ROIs were used to place the black (soft) and white (hard) areas in the virtual touch imaging. The ROIs were placed within the borders of the lesion, and the SWV values were automatically quantified in meters per second (m/s). The mean SWV value was obtained by averaging the SWV values measured. Lesion stiffness was measured by SWV imaging at up to 10 m/s.

Histopathological Examination and Elastosis Scoring

US-guided tru-cut biopsy was performed in breast lesions categorized as BI-RADS 4-5. For the tru-cut biopsy, a 14-gauge-thickness, 10-cm-long, fully automatic biopsy needle was used. The number of samples varied between 4–8 according to lesion size.

Elastin fibers are ECM components and are defined by their elasticity scores in breast lesions. The paraffin blocks of patients diagnosed with invasive ductal carcinoma and fibroadenoma were used for scoring elastin fibers. Four-micron thick sections were prepared and elastin stain was applied to all sections. Evaluation and scoring of elastin fiber content was evaluated by a pathologist, blinded to the US elastography results of the lesions. The amount of elastin fibers in the tumor stroma was scored (score: 0–3) according to the system of Shivas and Douglas (13). Tumors without elastin fibers were assigned a score of 0, those with thin elastin fibers or rim-shaped elastin around the duct were given a score of 1, lesions with thicker elastin fiber areas were assigned a score of 2, and those with large elastin fiber deposits in the tumor area were given a score of 3. The lesions were further categorized into two groups according to their elastin fiber content; those with a score of 0–1 were categorized as the low-score sub-group, and lesions with a score of 2–3 were categorized as the high-score sub-group. The pathologist who scored the elastin fiber content of the tumors was blinded to the other characteristics of the patients.

In addition, all benign lesions were analyzed according to their size by measuring the long axis diameter as either shorter than 2 cm or longer than 2 cm using. US images. The relationship between size and SWV and elasticity scores was analyzed. Malignant lesions were measured by ultrasonography in cm and lymph node status was investigated by US and positron emission tomography (PET). Malignant lesions were classified according to tumor diameter (under 2 cm as T1, 2–5 cm as T2, and >5 cm as T3). The relationship between tumor size and lymph node status with elastin scores was evaluated.

Histological grading was performed according to the Scarff-Bloom-Richardson system in malignant lesions (14). Grade 1–2 malignant lesions were considered as low grade, grade 3 malignant lesions as high grade.

Statistical Analysis

Descriptive statistics include mean and, standard deviations, and minimum and maximum values. A chi-square test was used for the distribution of elastosis scores in malignant lesions and fibroadenomas. Also, a chi-square test was used for the correlation of malignant lesion grade with elastin fiber scores. The Independent Samples t-test was used to compare the mean SWV between groups. The Statistical

Package for the Social Sciences software, version 13.0 was used for analysis (SPSS Inc., Chicago, IL, USA).

Results

Two hundred and fifty-five patients with a breast mass and with histopathological diagnosis were evaluated. Eighty-eight breast lesions that were diagnosed as proliferative and non-proliferative breast lesions, mastitis, and ductal carcinoma *in situ* (DCIS) were excluded. This resulted in a total of 167 patients being included in this study, subdivided into 92 (55.1%) with fibroadenoma and 75 (44.9%) with an invasive malignant breast mass. The mean age of the patients was 51.5±11.9 years in the malignancy group, and 33.6±12.3 years in the fibroadenoma group, which was significantly different (p = 0.001). Sixty-eight of the malignant lesions were invasive ductal cancer and seven were invasive lobular cancer. The mean SWV value was significantly greater at 6.10±1.6 m/s in the invasive cancer group compared to 3.32±1.0 m/s in the fibroadenoma group (p = 0.001). The SWV values in older patients with fibroadenoma was significantly greater (p<0.05) than in younger patients with fibroadenoma; <40 years old mean SWV 3.17±0.74 m/s vs above 40 years old: 3.61±1.36 m/s in patients aged >40 years.

The malignant lesions had significantly higher elastin fiber scores than fibroadenomas (p = 0.001) (Table 1 and Figures 1a and b). There was no correlation between the mean SWV value of malignant lesions and elastin fiber score (p = 0.175). However, low-grade lesions showed a higher elasticity score, and so elastin fiber score was found to be negatively correlated (p = 0.01) with grade of malignancy (Table 2). Malignant lesion size and lymph node status were not associated with the elastin fiber score (Table 3).

The mean SWV of fibroadenomas with low elastin fiber score was higher than the mean SWV of fibroadenomas with high elastin fiber score (p = 0.02) (Figures 2a–c, 3a–c and Table 4). A significant correlation was found between fibroadenomas size and elastin fiber score (p = 0.03). Fibroadenomas smaller than 20 mm in diameter were softer than ones with a larger diameter (>20 mm), and elastin fiber scores were higher (p = 0.001). Thus, there was a positive correlation between the size of fibroadenomas and the SWV, and an inverse correlation with the elastin fiber score (Table 5). However, no statistically significant correlation was found between breast cancer tumor size and elastin fiber score (p>0.05).

Discussion and Conclusion

This study has shown that the amount of elastin fiber in fibroadenomas was significantly less than that in malignant lesions. Furthermore, although the mean SWV value of malignant lesions was not correlated with the amount of elastin fiber present, the low SWV values of fibroadenomas was correlated with larger amounts of elastin fibers.

Elastin is an important ECM protein that provides elasticity to tissues and organs (1). Breast carcinoma cells stimulate the proliferation of stromal cells and promote elastin production (15). In breast cancer, elastin is present, both as individual fibers in the stroma and as large aggregates around the ducts or small blood vessels (7). The structural elements of tissues consist of structural proteins, including collagens, laminins, and elastin. During the tissue cycle, there is a balance between the formation and degradation of these proteins to ensure tissue health and homeostasis (1). Elastin and other ECM proteins interact with cancer cells (15, 16). Imbalances in the cycling of ECM proteins can lead to fibrosis, which can affect almost any organ or tissue. During fibrosis all structural elements, including collagen, laminin and elastin may be involved (1, 7). In this study, the lack of a significant correlation between the mean SWV value of malignant lesions and the elastin fiber score means that it is unreliable to use the elastin fiber score as a marker of SWV, possibly due to the effects of other ECM structural proteins on SWV measurements.

Chaming's et al. (17) reported that the stiffness of a breast invasive ductal carcinoma is associated with fibrosis. Also, connective tissue formation is increased in carcinomas (17-19). Lee et al. (10) revealed

Table 1. Elastin fiber scores according to histopathology

Elastin fiber score	Invasive cancer		Fibroadenoma	
	n (%)	*p*-value	n (%)	*p*-value
Low elastin score (0–1)	16 (21.3%)	0.001	79 (87%)	0.001
High elastin score (2–3)	59 (78.7%)		13 (13%)	
Total	75 (100%)		92 (100%)	

n: number

Table 2. Correlation of elastin fiber scores according to grade of invasive cancer

Elastin fiber score	Low grade invasive cancer n (%)	High grade invasive cancer n (%)	*p*-value
Low elastin score (0–1)	10 (16.1)	6 (46.2)	0.01
High elastin score (2–3)	52 (83.9)	7 (53.8)	
Total	62 (100)	13 (100)	

n: number

that malignant lesions have a harder structure than benign lesions and that the most important ECM protein providing this stiffness is collagen. As has been shown by this and earlier studies, malignant breast lesions also contain more elastin fiber than benign breast lesions (4, 20).

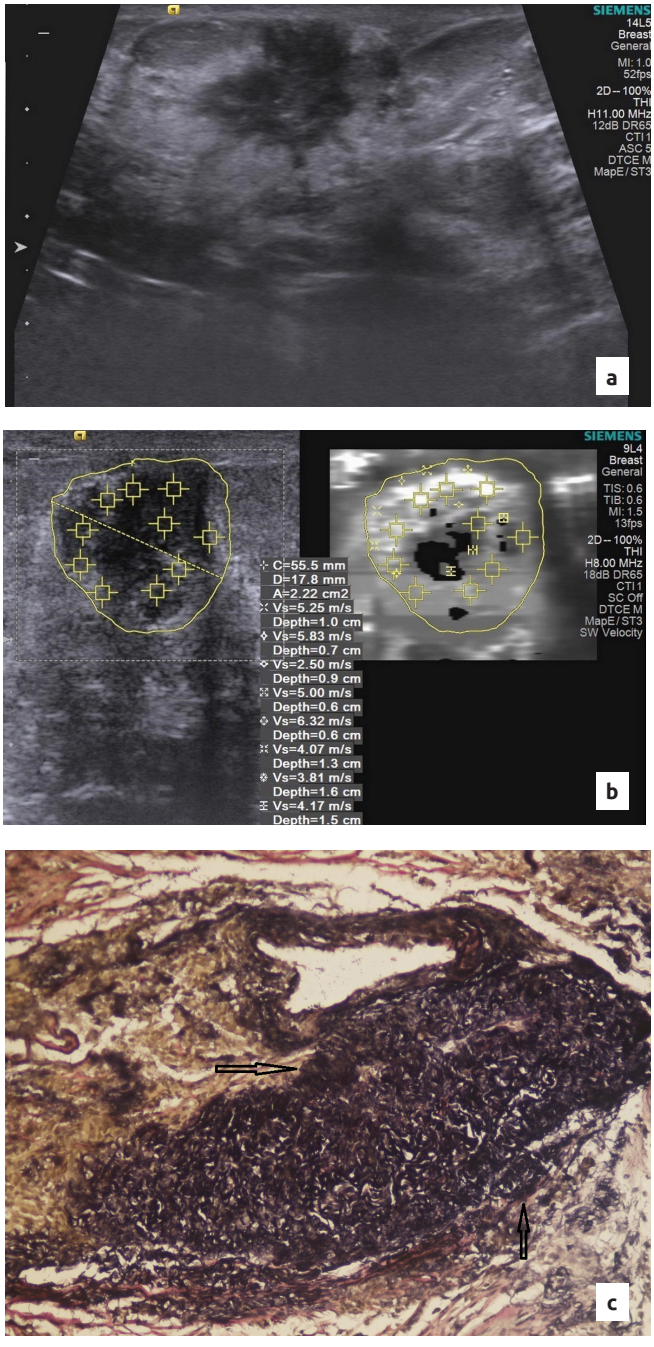

Figure 1. A 47-year-old patient with breast cancer. ARFI elastography of the lesion and elastic fiber appearance. **a)** BI-RADS 5 lesion on B-mode US, in non-parallel orientation, with irregular shape, and with a spicular margin feature. **b)** ARFI elastography imaging, showing high stiffness (mean SWV: 4.6 m/s). **c)** Elastin fiber dye (×200), elastin fiber areas in the form of large solid foci (red), which were distributed around tumor cell islands (up and right arrows). This was scored 3 according to the amount of elastic fibers.

ARFI: acoustic radiation force impulse; BI-RADS: Breast Imaging Reporting and Data System; US: Ultrasonography; SWV: shear wave velocity

In some studies, investigating elastin in breast cancer, elastin content was found to be correlated with low-grade breast cancer, estrogen receptor, negative human epidermal growth factor receptor 2 (HER-2), and low Ki-67 scores (20). In our study, low-grade cancers also showed high elastin fiber scores. Hence, elastin may be associated

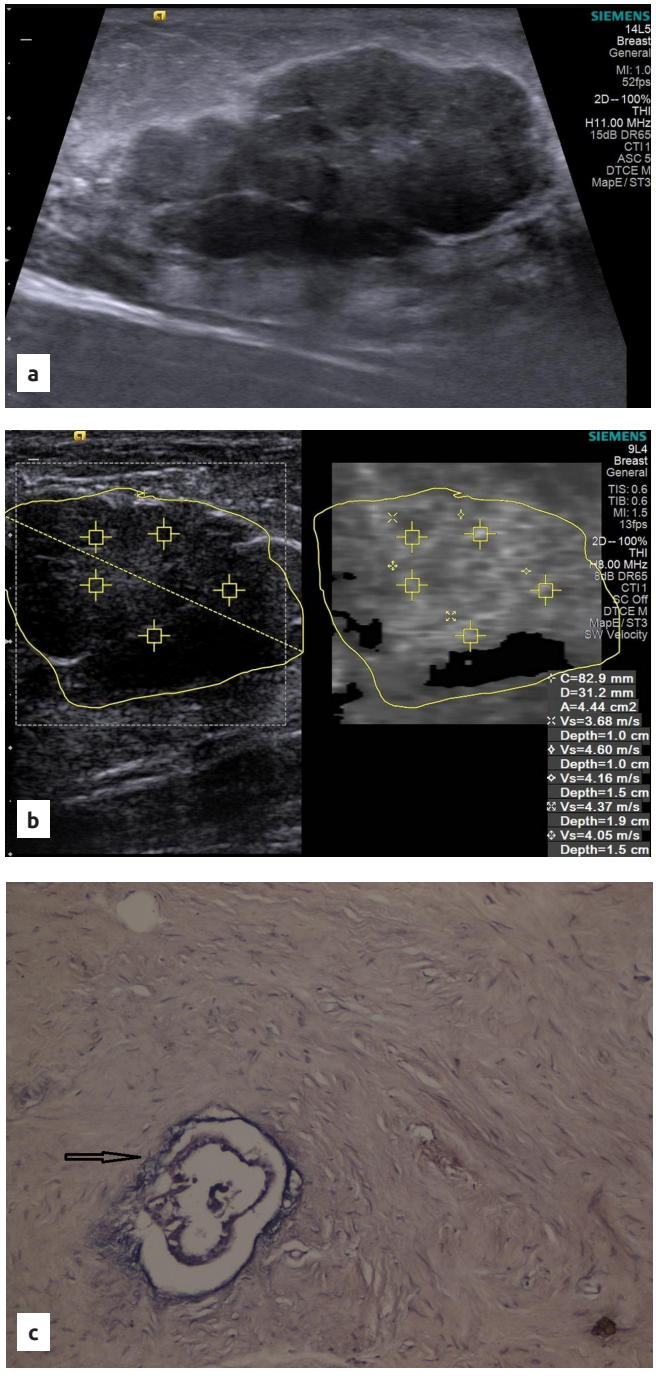

Figure 2. A 22-year-old patient. ARFI elastography and elastin fiber appearance of the lesion, which was pathologically confirmed as fibroadenoma. **a)** BI-RADS 4A lesion on B-mode US, in parallel orientation, with oval shape and lobular margin. **b)** ARFI elastography imaging, showing high stiffness (mean SWV: 4.1 m/s). **c)** Elastin fiber dye (×200). Thin, sparse elastin fibers (red), which were distributed around the ductus and stroma (right arrow). This was scored 1 according to the amount of elastin fibers.

ARFI: acoustic radiation force impulse; BI-RADS: Breast Imaging Reporting and Data System; US: Ultrasonography; SWV: shear wave velocity

with a better prognosis in invasive breast cancer. In our study, the absence of a relationship between elastin fiber score and breast cancer SWV values indicated that elastin fibers do not appear to contribute to tissue stiffness, and this supports the hypothesis that other ECM proteins are related to malignant lesion stiffness. In addition, the absence of correlation between tumor size and lymph node status with elastin fiber score is consistent with other studies in the literature (20). However, Chen et al. (20) found that tumor size and frequency of lymph node involvement were somewhat increased in interval tumors compared with for cancers detected by screening, and that interval tumors altogether lacked elastosis compared to those detected by screening. Therefore, the absence of elastosis has been associated with a poor prognosis.

Mera and Davies (21) showed that benign breast lesions had a significantly smaller average amount of elastin fiber than malignant lesions, implicating the elastin fiber content in the progression of breast carcinoma. Liu et al. (11) reported that the average collagen and elastin fiber areas were correlated with the maximum elasticity of breast lesions and that malignant lesions had higher collagen and elastin fiber contents than benign lesions. However, their work made no distinction concerning the extent to which collagen and elastin

Table 3. Correlation of elastin fiber scores with nodal status and tumor diameter of invasive cancer

Nodal status	Elastin fiber score		*p*-value
	Low elastin score (0–1)	High elastin score (2–3)	
N0, n (%)	0 (0.0)	7 (11.9)	0.49
N1, n (%)	7 (43)	33 (44)	
N2, n (%)	4 (25)	17 (22.7)	
N3, n (%)	5 (31)	18 (24.7)	
Tumor diameter			
T0, n (%)	0 (0.0)	0 (0.0)	0.89
T1, n (%)	6 (37.5)	24 (40.7)	
T2, n (%)	7 (43.8)	33 (55.9)	
T3, n (%)	3 (18.8)	2 (3.4)	
T4, n (%)	0 (0.0)	0 (0.0)	

n: number; N: node; T: tumor

Table 4. Comparison of elastin fiber scores and SWV of malignant breast lesions and fibroadenomas

Elastin fiber score	Invasive cancer		Fibroadenoma	
	Mean SWV (m/s) ± SD	*p*-value	Mean SWV (m/s) ± SD	*p*-value
Low elastin score (0–1)	5.571±1.9	0.175	4.23±1.5	0.02
High elastin score (2–3)	6.230±1.5		3.17±0.8	
Total	6.11±1.63		3.32±1.0	

SWV: shear wave velocity; SD: standard deviation

Table 5. The value of SWV and elastin fiber score of fibroadenomas according to lesions size

Fibroadenoma size	n (%)	Mean SWV (m/s) ± SD	p-value	Low elastin score (0–1), n (%)	High elastin score (2–3), n (%)	p-value
Diameter (<20 mm)	33 (35.9%)	2.87± 0.724	0.001	25 (24.2%)	8 (75.8%)	0.03
Diameter (≥20 mm)	59 (64.1%)	4.12 ± 0.96		54 (91.5%)	5 (8.5%)	

SWV: shear wave velocity; SD: standard deviation; n: number

contribute to flexibility (11). The fact that soft fibroadenomas in our study had more elastin fibers than harder adenomas may indicate that elastin supports flexibility in the tissues. However, Shi et al. (5) showed that the shape and aggregation of the fibers, as well as the amount of ECM components, were related to the stiffness of breast lesions. In our study, the amount of elastin fibers was taken into consideration, and no assessment of the arrangement of elastin fibers was made.

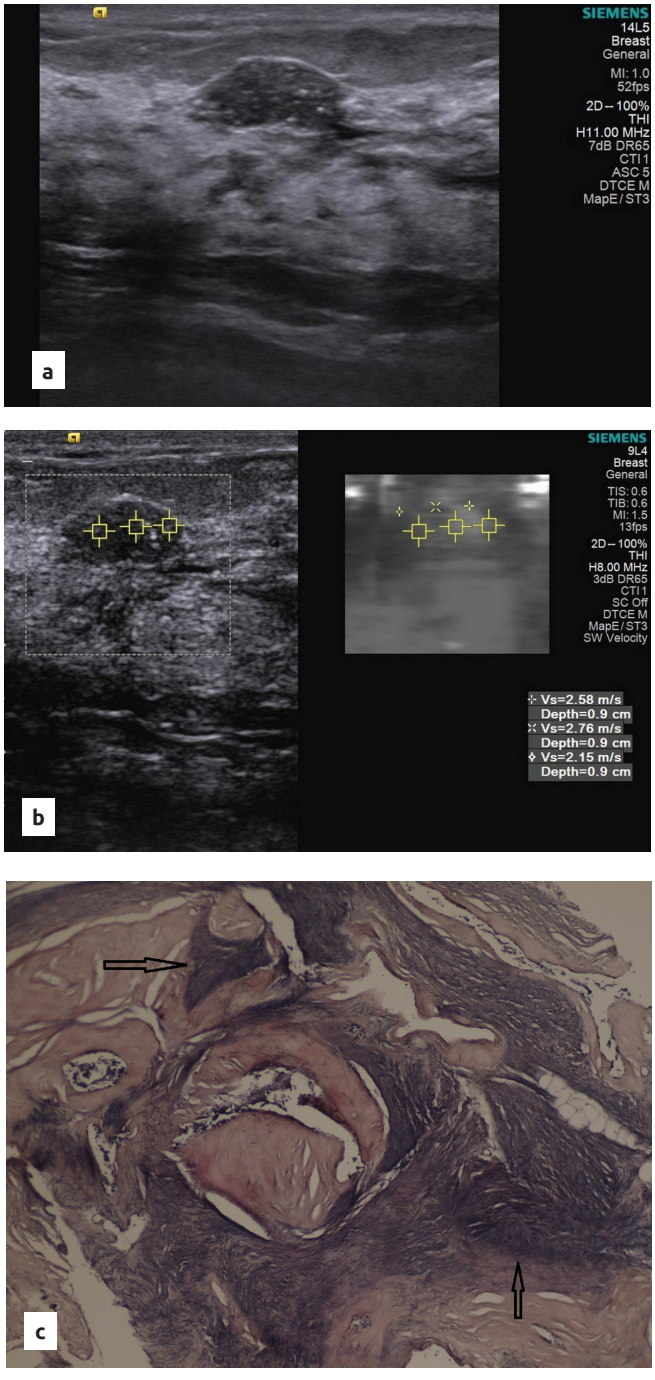

Figure 3. A 35-year-old patient. ARFI elastography and elastin fiber appearance of the lesion, which was pathologically confirmed as fibroadenoma. **a)** BI-RADS 4C lesion on B-mode US, in parallel orientation, with oval shape and a minimally irregular and angular margin. Foci of microcalcification are observed within the lesion. **b)** ARFI elastography imaging, showing low stiffness (mean SWV: 2.5 m/s). **c)** Elastin fiber dye (×100). Large foci of elastin fibers (red), which were distributed in the mesenchyme (up and right arrows). This was scored 3 according to the amount of elastin fibers.

ARFI: acoustic radiation force impulse; BI-RADS: Breast Imaging Reporting and Data System; US: ultrasonography; SWV: shear wave velocity

The amount of elastin fibers in fibroadenomas is reportedly slightly less than in breast carcinomas (22-24). In benign breast lesions, especially in sclerosing adenosis, myoepithelial cell proliferation suggests that the myoepithelium plays a role in elastin fiber synthesis (9). Elasbali et al. (25) detected elastin fibers in areas of fibrocystic change and fibroadenoma-like lesions.

The present study found that the harder and larger fibroadenomas contained fewer elastin fibers. Moreover, large fibroadenomas were found to have a harder structure, which is consistent with the literature (26). So, this finding suggests that, as fibroadenomas increase in size, elastin fibers in the stroma are replaced by other proteins present in the ECM. Lee et al. (27) showed that the hardness of fibroadenomas measured by elastography was associated with hyaline degeneration. The increase in fibroadenoma stiffness with age may be related to a low elastin fiber score, suggesting that the amount of the other stromal components in lesions increases with age.

There are a number of limitations of this study. The most important limitation of our study was that the correlation of elastin fiber score with other ECM proteoglycans, such as collagen, laminin, and fibronectin was not evaluated. In addition, no assessment was made of the arrangement of the elastin fibers within the surrounding tissues, which will affect the ability of these long, linear proteins to function as normal. More extensive studies should be conducted to investigate other ECM components in malignant lesions and their relationship to the prognosis and radiological appearance of malignant lesions. As only core biopsy samples were tested for elastin in this study, there could be potential sampling error. More accurate results may be obtained by studying excisional biopsy samples. In our study, the amount of elastic fibers in fibroadenoma subtypes was not examined separately and therefore does not provide information about the elastic fiber content of different histological types of fibroadenomas. A number of fibroadenoma variants are known, including juvenile, giant, complex, myxoid, cellular, and hyalinized fibroadenomas (28). Since these variants have different clinical behaviors, the potential for malignant transformation, and treatment strategies, the diagnosis of specific variants is important. With more specific future studies in this area, it will be possible to know the elastin fiber behavior in the ECM structure of fibroadenomas, especially complex fibroadenomas that are known to have a 3.1-fold increase in elastin content compared with the other fibroadenomas (29). This would provide more information about the optimal diagnostic and therapeutic approaches for all fibroadenomas. In our study, only quantitative SWV measurements were used during elastography. The lack of qualitative SWE evaluation is another limitation.

In conclusion, the relationship between elastin fiber score in fibroadenomas and malignant lesions was investigated. Low-grade breast cancers were associated with high elastin fiber scores, so elastin may be a prognostic marker for breast cancer. In addition, there was an inverse correlation between SWV values and the elastin fiber score in fibroadenomas, and thus variable elastin fiber content in this heterogeneous group of fibroadenomas might explain why SWV values of fibroadenomas are very variable. Finally, it may be possible to use, an elastin fiber score for differentiating fibroadenomas from malignancy but further studies are needed to make this accurate.

Ethics Committee Approval: The study was approved by Van Yüzüncü Yıl University Ethics Committee (decision number: 2020/03-09, date: 22/05/2020).

Informed Consent: Patient consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.T.; Design: A.Y.; Supervision: İ.A., A.Y.; Data Collection and/or Processing: İ.A., O.T., A.Y.; Analysis and/or Interpretation: A.M.G.; Literature Search: O.T., A.M.G.; Writing: N.T.; Critical Review: N.T.

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