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Shear-Wave Elastography-Guided Core Needle Biopsy for the Determination of Breast Cancer Molecular Subtype

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Objective—To investigate whether shear-wave elastography (SWE) guidance during core-needle biopsy can improve diagnostic accuracy and accurate determination of the molecular subtypes of breast cancer.

Methods—This controlled, randomized prospective cohort study included 58 patients (mean age: 56.9 ± 16.2) who were referred for image-guided core-needle biopsy between May 2018 and April 2019 for lesions larger than 1 cm. In Group 1, 30 lesions were biopsied without SWE guidance and recorded as Biopsy A. In Group 2, 30 lesions were examined with SWE before biopsy, and then two different parts of the lesions were biopsied; biopsies from the relatively rigid areas of the lesions were recorded as Biopsy B, and biopsies from the less rigid areas of the lesions were recorded as Biopsy C. The histopathological and immunohistochemical results of biopsies were compared with the surgical results.

Results—The sensitivity of Biopsy A, B and C were 96.7%, 100% and 100%, respectively. The benign-malignant concordance rates were 94.7%, 100%, and 90% and the diagnostic concordance rates were 89.5%, 100%, and 90% in Biopsies A, B, and C, respectively. When the 10% differences in the estrogen receptor (ER), progesterone receptor (PR), and Ki67 rates were considered significant, the concordance rate of ER was highest in Biopsy B (77.8%; p = 0.040). The concordance rate of immunohistochemical subtyping was 100% in Biopsy B and 71.4% in Biopsies A and C (p = 0.086).

Conclusion—SWE-guided core-needle biopsy of breast lesions increased the sensitivity, diagnostic accuracy, and accuracy of immunohistochemical subtyping to 100%.

Key Words—breast cancer; core-needle biopsy; immunohistochemical markers; molecular subtype of breast cancer; shear-wave elastography

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Abbreviations

BIRADS, Breast Imaging and Reporting Data System; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SWE, shear-wave elastography; US, ultrasound

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Introduction

Breast cancer is the most common cancer of women worldwide, and it is the second-leading cause of death following lung cancer. Treatment options for breast cancer have changed in recent years; primary conventional surgery is no longer considered the most appropriate option for every patient. The molecular subtype of the tumor, the spread of the tumor, and patient preference are the main determinants of breast cancer

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treatment, and a multidisciplinary approach is necessary. The most important determinant of systemic breast cancer treatment is the molecular subtype of the tumor; for example, it is generally preferred to use endocrine therapy in cases of hormone receptor positivity, anti-HER2 drugs in cases of human epidermal growth factor receptor 2 (HER2) positivity, and chemotherapy in triple-negative patients. The molecular subtype also determines recurrence and prognosis. For example, the triple-negative subtype shows recurrence more frequently than other subtypes, while the luminal A subtype has a better prognosis. The molecular subtype of breast cancer is determined by studying estrogen receptor (ER), progesterone receptor (PR), HER2 status, and Ki67 proliferation indexes derived from biopsy materials.[1-7] Breast cancer is divided into 4 main subtypes: luminal A (ER+ or PR+, HER2-, and Ki67 < 15%), luminal B (ER+ or PR+, HER2−/+, and Ki67 > 15%), triple negative (ER-, PR-, and HER2-), and HER2+ (ER-, PR-, and HER2+).[8] Biopsy results play a crucial role in determining the treatment protocol.[5,7,9]

Ultrasound (US) is an important modality for the detection and characterization of breast masses; it is also the first guiding method to be chosen for percutaneous biopsies in daily practice. Elastography is a US-based imaging modality recently developed to measure the elasticity of tissues using sound waves. Two-dimensional shear-wave elastography (SWE) is the newest method of monitoring and measuring the real-time stiffness of the tissue superimposed on the B-mode image.[10-14] The elasticity of tissues increases in many specific cases, such as in cases of solid tumors as a pathological process or in cases of fibrosis as a physiological process.[15] Previous studies have also shown that the breast cancer subtype is a determinant of tissue stiffness.[16,17]

Core-needle biopsy is a widely used, reliable method for the diagnosis of breast cancer, used mainly on Breast Imaging and Reporting Data System (BIRADS) 4 and 5 lesions. Despite the many advantages of core-needle biopsy, it does not always completely and consistently reflect the biological features of the examined tumor due to intratumoral heterogeneity and methodological flaws. Previous studies have shown that consistency after resection by biopsy decreases to 77.8% for ER, 69% for PR, and 60% for HER2.[18-22] Elastography-based biopsy, which has been practiced for years in the diagnosis of prostate cancer, increases sensitivity as well as specificity and reduces the need for re-biopsy.[23] To the best of our knowledge, there have been no prior studies on the use of elastography in the biopsy of breast lesions.

The aim of the present study was to investigate the role of SWE-guided core-needle biopsy of breast masses for the accurate determination of immunohistochemical breast cancer subtypes.

Materials and Methods

This controlled, randomized prospective cohort study was held at our institute between May 2018 and April 2019. The study was approved by the institutional ethics committee and funded by the University Department of Scientific Research Projects.

Study Population

Patients referred to our unit between May 2018 and April 2019 for core-needle biopsy were included in the present study.

Inclusion criteria:

- Patients over the age of 18 years.
- Patients with BIRADS 4 or 5 imaging findings.
- Patients with lesions greater than 1 cm in size.
- Patients who consented to the procedure.

Exclusion criteria:

- Patients under the age of 18 years.
- Patients with lesions less than 1 cm in size.
- Patients with history of surgery for the same lesion.
- Patients who did not consent to the procedure.

A total of 60 biopsies were performed, including 30 biopsies in Group 1 and 30 biopsies in Group 2. Patients were divided into these 2 groups by block randomization. Specifically, patients who had been referred within the first and third months of the study period were included in Group 1, and patients who had been referred within the second and fourth months of the study period were included in Group 2.

Prior to the biopsy procedure, the BIRADS categories of the lesions (according to the BIRADS lexicon version 5) were determined with US and/or

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mammography images by 2 radiologists with 20 years (P.B.) and 5 years (I.B.A.) of experience in the field of breast radiology.

Biopsy Procedures

Prior to the biopsy procedures, the participants were evaluated according to the consensus guidelines endorsed by the Cardiovascular and Interventional Radiological Society of Europe.[24] The procedures used for patients with anticoagulant-antiaggregant drug use or those prone to bleeding were regulated according to this guideline.

The biopsies were performed under standard sterile conditions with local anesthesia. An automatic 16G core-needle biopsy gun (BARD MAX-CORE) was used for all patients. The firing distance of the needle was 22 mm, and the sampling length was 17 mm.

All biopsies were performed by the same fifth-year radiology resident (Ahmet Peker), who had received certification to carry out advanced non-vascular interventional procedures from the Turkish Society of Interventional Radiology. The Siemens Acuson S3000 US system (Siemens Medical Solutions, Mountain View, CA) was used with a 9 L4 linear transducer for all biopsies, and Virtual Touch IQ software was used for elastography.

In Group 1, 4 core-needle biopsy samples were obtained from the lesions without SWE guidance and labeled Biopsy A. In Group 2, elastographic evaluation of the target lesions was performed prior to the biopsy procedure. The stiff areas of these lesions were identified and differentiated using these images. Biopsies were planned for 2 different areas of the lesions, one with most stiffness and another with the less stiffness (Figure 1). Elasticity values were measured in meters/seconds with multiple ROIs from these areas, and these measurements were averaged. Areas that could not be measured due to the shielding artefact were accepted as having the maximum value of stiffness (10 m/s). Then, 3 core-needle biopsy samples were obtained from these determined areas through a single incision. Samples derived from the relatively rigid areas of the lesions were recorded as Biopsy B, and samples derived from the less rigid areas of the lesions were recorded as Biopsy C (Figure 2). Finally, all the samples were fixed with a formalin solution and sent to the pathology department.

Pathological Analysis

All samples were evaluated by the same pathologist (D.G.), who had 15 years of experience in the field of breast pathology. In this analysis, the lesions were diagnosed and the immunohistochemical results (immunohistochemical subtypes, ER and PR percentages, Ki67 values, and HER2 statuses) of the malignant lesions were recorded.

The pathology results of the patients who were operated upon were recorded, and the biopsy and post-surgical pathology results of both groups were compared in terms of diagnoses and immunohistochemical markers. Immunohistochemical comparisons were not performed for the patients who had received chemotherapy or radiotherapy prior to the operation. The results for Biopsies B and C, which were obtained from the same lesion in Group 2, were compared as well.

Results

Demographic Characteristics of the Study Population

Core-needle biopsies were performed in 58 patients, including 1 male and 57 female patients. The mean patient ages were 57.7 (±18.5) years in Group 1 and 56 (±13.7) years in Group 2. The mean lesion diameters were 33.2 mm (±22.6) in Group 1 and 27.8 mm (±11.9) in Group 2. There were no statistically significant differences between the 2 groups in terms of age or lesion size ($p = 0.900$ and $p = 0.908$, respectively). In Group 2, 4 biopsies were performed on 2 different lesions from 2 patients.

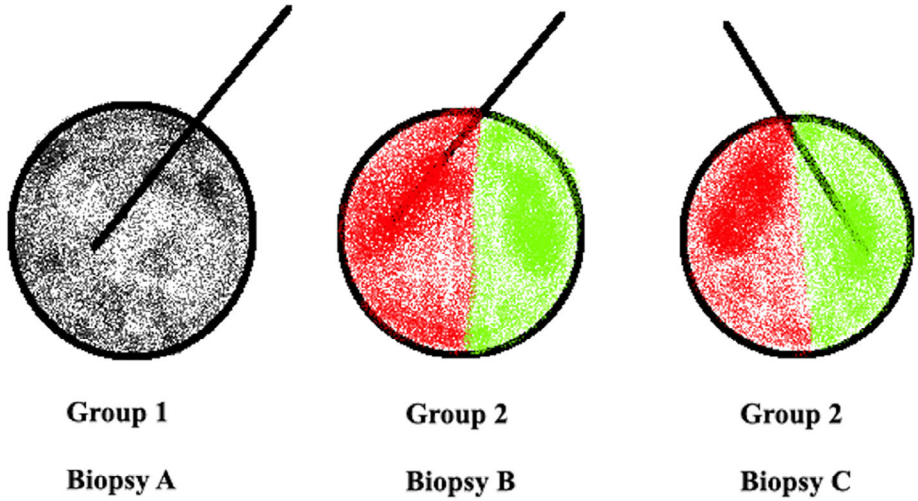
B-Mod Ultrasound and Elastographic Findings

In Group 1, 22 (73.3%) lesions were categorized as BIRADS 5, 3 (10%) lesions were categorized as BIRADS 4C, 4 (13.3%) lesions were categorized as BIRADS 4B, and one (3.3%) lesion was categorized as BIRADS 4A. In Group 2, 24 (80%) lesions were categorized as BIRADS 5, 3 (10%) lesions were categorized as BIRADS 4C, and 3 (10%) lesions were categorized as BIRADS 4B.

Elasticity values (i.e., SWE speed averages) were measured in the areas from which biopsies B and C were taken, and the difference between the elasticities of the 2 areas was calculated for each lesion. The mean shear-wave velocities were 6.41 ± 1.86 m/s in

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Figure 1. Schematic representation of biopsies.

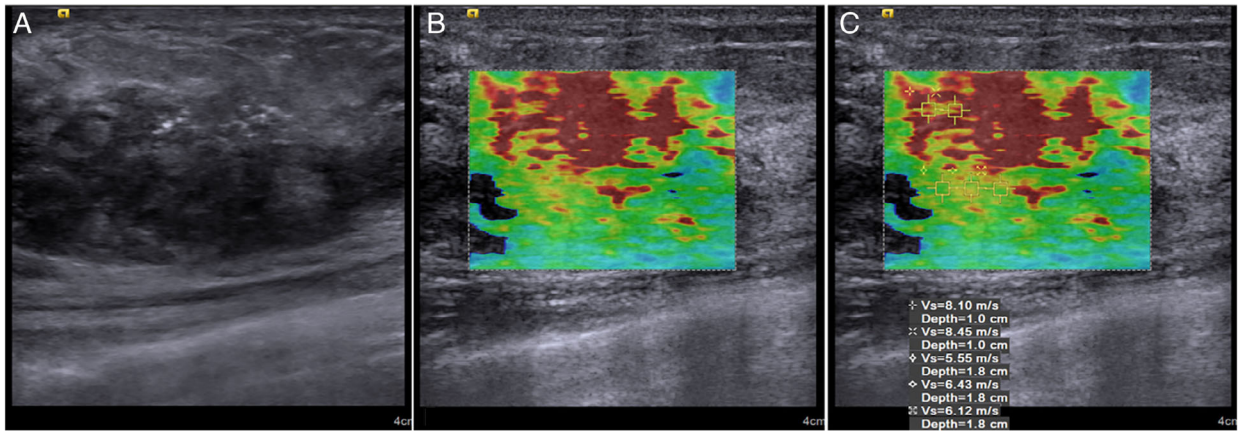


Biopsy B and 4.24 ± 0.96 m/s in Biopsy C. The mean difference between the 2 areas was 2.16 (±1.36) m/s. There was no statistically significant correlation between the differences in the elasticities of the biopsied areas and the observed immunohistochemical inconsistencies (ER p = 0.995, PR p = 0.404, Ki67 p = 0.382, and subgroup p = 0.214; point double series correlation).

Histopathological Results

The obtained diagnoses are summarized in Table 1. None of the Biopsy A, B, or C samples were deemed insufficient. One biopsy result was inconclusive in Group 1, and the rest of the biopsies diagnosis was given. This inconclusive biopsy was performed for a BIRADS 5 lesion, which measured 12 mm in its longest diameter; 4 cm of white-grey tissue from this biopsy was sent to the pathology lab. No malignant-benign distinction could be made in the pathological evaluation, and excisional biopsy was recommended. As a result of excisional biopsy after wire marking, the lesion was diagnosed as mixed-type invasive breast carcinoma. Diagnoses were made for all the lesions in Biopsies B and C.

Figure 2. Thirty-nine-year-old female patient with BIRADS-5 lesion in the right breast. (**A**) B-mode-ultrasound image of the lesion. (**B**) Elastogram image for determining the different stiffness areas of the lesion. (**C**) Stiffness measurement of biopsy planned areas in the lesion.



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Table 1. Histopathological Diagnosis of the Biopsies

		Biopsy A		Biopsy B		Biopsy C	
		N	%	N	%	N	%
Diagnosis	Benign	2	6.7	1	3.3	4	13.3
	Malignant	27	90	29	96.7	26	86.7
Malignant	DCIS	1	3.3	1	3.3		
	İDC	20	66.7	23	76.7	20	66.7
	İLC	4	13.3	3	10	2	6.7
	Other	2	6.7	2	6.7	2	6.7
Benign	Fibrosis					2	6.7
	Intraductal Papilloma	1	3.3				
	Phyllodes Tumor	1	3.3	1	3.3	1	3.3
	Ductal Epithelial Hyperplasia					1	3.3

The sensitivity was 96.7% in Biopsy A and 100% in Biopsies B and C (p = 0.317).

Of the 30 lesions across both groups, 19 from Group 1 and 20 from Group 2 were surgically removed. When the biopsy results were compared with the surgical results, the concordance rate was highest in Biopsy B (100%; p = 0.355). The benign-malignant and diagnostic concordance rates are summarized in Table 2. One patient in the Biopsy A group received intraductal papilloma as a result of the biopsy; the surgical result in this case was diagnosed as a papillary subtype of invasive ductal carcinoma. In Group 2, Biopsies B and C were taken from different areas of the same lesion with different stiffness values, showing different diagnoses in 3 lesions (10%) and the same diagnosis (90%) in 27 lesions. In one of these lesions, ductal epithelial hyperplasia was diagnosed in Biopsy C while invasive lobular carcinoma was found in Biopsy B. In other patients, Biopsy C was diagnosed as fibrotic tissue while Biopsy B was diagnosed as invasive lobular carcinoma in one lesion and invasive ductal carcinoma in another. These 2 patients underwent surgery, and the surgical pathology results were consistent with Biopsy B (Table 3).

Immunohistochemical Markers

Patients who had received chemotherapy before surgery (n = 20) were not included in the comparison since chemotherapy changed the immunohistochemical markers of their tumors.[25] Of the 19 patients who were operated on in Group 1, 10 were operated on after chemotherapy and one was diagnosed with a phyllodes tumor. One lesion that resulted from biopsy was intraductal papilloma and was postoperatively diagnosed as invasive ductal carcinoma. For this reason, biopsy and surgical immunohistochemical markers were available in 7 patients. Of the 20 patients operated on in Group 2, 10 were operated on after chemotherapy and one was diagnosed with a phyllodes tumor. The remaining 9 patients presented with biopsy and surgical immunohistochemical markers. Since 2 of these 9 patients were diagnosed with fibrotic breast tissue in Biopsy C, immunohistochemical analysis was not performed for these 2 biopsies (Figure 3).

Table 2. Accuracy of Biopsies

		Benign-Malignant Concordance		Diagnostic Concordance		
		False	True	False	True	Total
Biopsy A	N	1	18	2	17	19
	%	5.3	**94.7**	10.5	**89.5**	100
Biopsy B	N	0	20	0	20	20
	%	0	**100**	0	**100**	100
Biopsy C	N	2	18	2	18	20
	%	10	**90**	10	**90**	100

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Table 3. Diagnostic Differences in Group 2

	Biopsy B	Biopsy C	Surgery
I	invasive lobular carcinoma	ductal epithelial hyperplasia	invasive lobular carcinoma
II	invasive ductal carcinoma	fibrosis	invasive ductal carcinoma
III	invasive lobular carcinoma	fibrosis	invasive lobular carcinoma

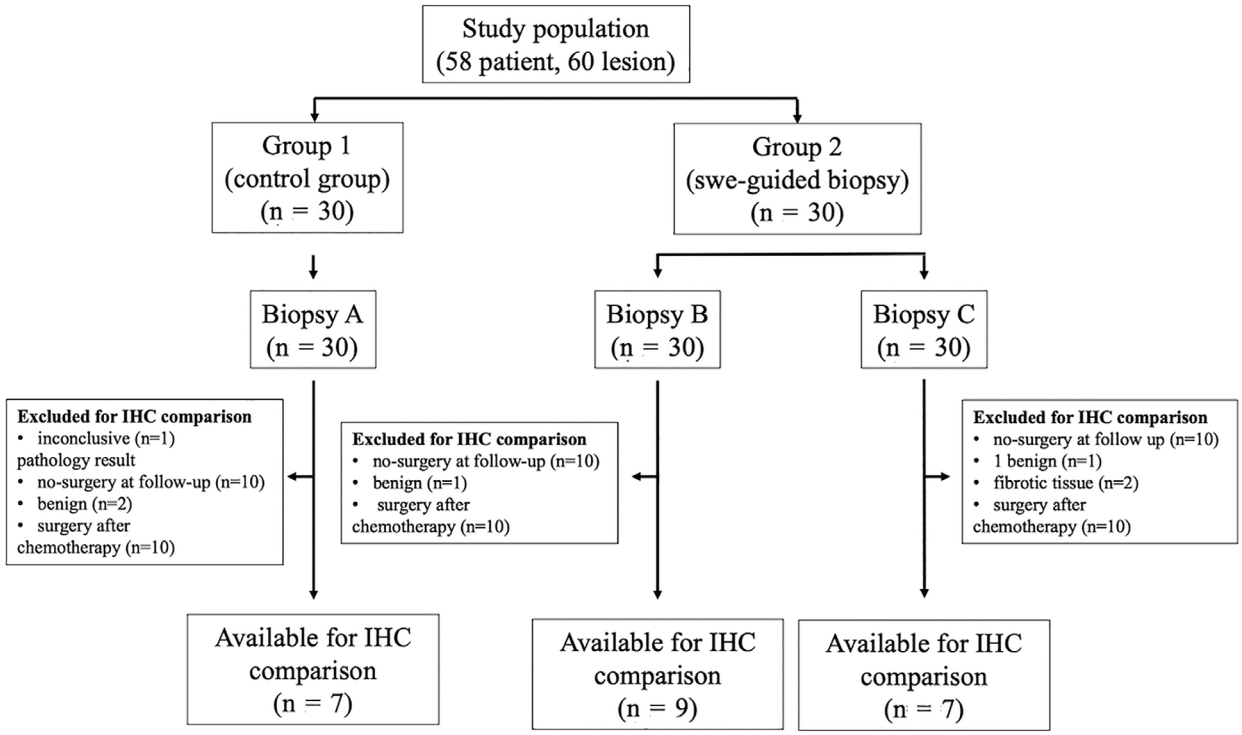
When the biopsy materials were compared with the surgical materials for ER positivity, PR positivity, and HER2 receptor positivity, one biopsy was inconsistent in the HER2 state. In the cases of ER and PR positivity, there were no inconsistencies. In the KI67 index, for which a difference of 10% or greater was considered significant, inconsistencies were observed in 12 biopsies. The distribution of the findings by groups is summarized in Table 4. There were no significant differences in the concordance rates of ER, PR, or HER2 positivity or the Ki67 indexes between the biopsy groups ($p = 0.082$ for HER2, $p = 0.838$ for Ki67).

Considering the positive percentages of ER and PR, for which a difference of 10% or greater was considered significant, the concordance between the groups is summarized in Table 4. The highest concordance rate in the ER ratio was found in the biopsy B group (77.8%), and a statistically significant difference was found between the groups ($p = 0.040$). There were no statistically significant differences in the rates of PR positivity ($p = 0.848$).

Immunohistochemical Subgroup Comparison

The effects of differences between immunohistochemical markers on lesion subtype were evaluated, and subtype inconsistency was detected in two lesions in Biopsies A and C (Table 4). The highest concordance rate was obtained from Biopsy B (100%; $p = 0.086$). As mentioned earlier, the subtype of

Figure 3. Flowchart of the study.



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Table 4. Immunohistochemical Markers Concordance in Biopsies

		Biopsy A		Biopsy B		Biopsy C	
		N	%	N	%	N	%
ER Status	False	0	0	0	0	0	0
	True	7	100	9	100	7	100
PgR Status	False	0	0	0	0	0	0
	True	7	100	9	100	7	100
Her 2 Status	False	1	14.3	0	0	0	0
	True	6	85.7	9	100	9	100
Ki67 Difference	No	4	57.1	4	44.4	4	57.1
	Yes	3	42.9	5	55.6	3	42.9
ER (+) Difference	No	1	14.3	7	77.8	3	42.9
	Yes	6	85.7	2	22.2	4	57.1
PgR (+) Difference	No	3	42.9	3	33.3	2	28.6
	Yes	4	57.1	6	66.7	5	71.4
Subgroup	False	2	28.6	0	0	2	28.6
	True	5	71.4	9	100	5	71.4

Biopsy A changed as the result of a change in HER2 status in one biopsy. In another biopsy, a patient classified as luminal A was reclassified as luminal B after surgery. In Biopsy C, 2 patients classified as luminal A were reclassified as luminal B after surgery.

Discussion

In the present study, the use of SWE guidance to take material from the stiffer areas of breast lesions through core-needle biopsy increased the sensitivity, diagnostic accuracy, and accuracy of immunohistochemical subtyping to 100% and increased the consistency rate in the ER ratio. Routine B-mode US-guided biopsy was used for the control group; in this way, it was provided to compare the biopsy of the relatively stiffer area of the lesion with routine US-guided biopsy. Biopsies on 2 different stiffness areas of the same lesion accompanied by elastography were also tested, and it was represented that elastography findings may cause differences within the same lesion. To the best of our knowledge, this study is the first in the literature to use elastographic guidance to increase the accuracy of diagnostic and immunohistochemical subtyping through core-needle biopsy of breast masses.

The use of US elastography for the diagnosis of breast lesions is promising, especially in BIRADS 4 lesions. Previous studies have reported that the addition of elastography to B-mode US increased the sensitivity of the malignant benign distinction of BIRADS 4 lesions by 96% and increased the specificity of this distinction by up to 95%.[18-22] Factors such as cellular activation of the tumor, apoptosis, amounts of fibroblasts and fibrosis, changes in the extracellular matrix, collagen structure, integrin, and focal adhesion kinase increase the stiffness of the tissues in malignant tumors.[16,26,27] Studies in the current literature have claimed that the stiffness of a tumor is also affected by its immunohistochemical subtype, hormone receptor status, and Ki67 indices; therefore, the immunohistochemical subtype of a tumor can be predicted based on its stiffness.[28,29]

Factors affecting the accuracy of core-needle biopsy have been described in detail in the literature. Such factors include the experience of the radiologist; the size, heterogeneity, localization, and depth of the lesion; and the amount of material taken.[6,30] Fishman et al. described the relationship between the number of samples taken by core-needle biopsy and the incidence of malignant cells within these samples.[31] In this study, Fishman et al. detected a malignant cell rate of 70% in one sample, 92% in 2 samples, 96% in 3 samples, and 100% in 4 samples and therefore recommended that at least 4 samples be taken for core-needle biopsy. Taking these suggestions into consideration, we took 4samples from US-guided biopsies and 3 samples from both sides of the lesions from elastography-guided biopsies.

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In the literature, the sensitivity of core-needle biopsy has been reported to be in the range of 85–100%.[32] In the present study, we calculated sensitivities of 96.7% for Biopsy A and 100% for Biopsies B and C; this finding is compatible with the literature. In a study by Makkun and colleagues, the diagnostic accuracy of biopsy with a 14G core-needle was found to be 95.65%.[33] In a retrospective study of 254 similar biopsies performed by Davidson et al., the diagnostic accuracy of core-needle biopsy was calculated as 91.3%.[34]

When accuracy was considered in terms of benign-malignant distinction in the present study, the concordance rates of Biopsies A, B, and C were calculated as 94.7%, 100%, and 90%, respectively. When accuracy was considered in terms of the given diagnosis, the accuracy of Biopsies A, B, and C were calculated as 89.5%, 100%, and 90%, respectively. The accuracy of Biopsy B—that is, the biopsy performed on the hard area of each lesion—was calculated as 100% in both cases. There was no statistically significant difference between the groups, possibly due to the low number of patients in the present study.

The accuracy of core-needle biopsy in comparison with surgical material has been reported in the literature to vary between 77.8% and 100% for ER, 69% and 97.1% for PR, and 60% and 98% for HER2.[35-37] In the present study, there were no inconsistencies in Biopsies A, B, and C with respect to the presence or absence of ER and PR positivity. With respect to HER2 status, inconsistency was detected in one patient in Biopsy A (14.3%). In the evaluation of 10% differences in the ER and PR ratios in the Ki67 index, the highest concordance rate was found in Biopsy B (77.8%) and a statistically significant difference was found between the groups ($p = 0.04$). The immunohistochemical subtyping concordance rates were 71.4% in Biopsy A and C and 100% in Biopsy B. While no similar studies have been reported in the literature, it is well known that tumoral heterogeneity affects biopsy accuracy.[6,30] Using elastography, taking samples from the areas that accurately represented the features of the lesions increased accuracy.

The size of a biopsied lesion can affect the sensitivity and accuracy of the biopsy.[6] In the present study, there were no statistically significant differences in terms of lesion size. Further, the same person performed all biopsies across both groups, and the same experienced pathologist evaluated all biopsy and surgical materials. Overall, there were no methodological differences between the groups that might have affected the results.

When biopsies from different hardness areas of the same lesion were compared in Group 2, 3 biopsies yielded different diagnoses (10%). However, no differences were found in the evaluation of immunohistochemical markers as present or absent. The evaluation of the biopsy materials at the same time and by the same pathologist may have affected this result. When a > 10% difference in ER, PR, and Ki67 rates was considered significant, 12.5%, 20.8%, and 29.2% differences were detected in patients diagnosed with malignancies in Group 2. These differences caused immunohistochemical subtyping differences in 3 patients (12.5%). Although no similar studies have been reported in the literature, it is well known that tumor size and heterogeneity can affect biopsy accuracy and that different immunohistochemical profiles can cause varying levels of stiffness.[6,28,29] In the present study, the patients who underwent biopsy were randomized. We anticipated that these differences would increase in large, heterogeneous lesions. In Group 2, there were no statistically significant correlations between differences between the mean SWE speeds of the biopsied areas and differences in diagnosis or immunohistochemical subtyping. This finding may have been due to the limited number of patients included in this study.

The present study had some limitations, including the low number of included patients, the fact that not every patient with a malignant diagnosis was operated on, and the fact that the presence of patients receiving chemotherapy before surgery reduced the number of patients for comparison of immunohistochemical markers. The examination of all materials by a single pathologist also served as a limitation, as the pathologist may have been affected by their findings from other materials, especially in the evaluation of 2 different samples from Group 2 that they knew to be from the same lesion. Experience is needed to properly take samples from relatively hard areas of lesions and direct a needle to a target area. In addition, the needle used in the present study had a firing distance of 22 mm and a sampling length of 17 mm, which may have resulted in sampling from surrounding tissue for smaller target areas. Further, the local

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anesthetic agent given before the procedure and bleeding due to previous biopsies may have caused changes in the appearances of the lesions. Therefore, the person performing the biopsies should have dominated the appearance and elastographic features of the lesions prior to biopsy.

The strengths of the present study included the prospective design, the fact that all biopsies were performed by the same person with the same protocol, and randomization between groups.

Conclusion

In conclusion, SWE-guided core-needle biopsy of breast lesions increased the sensitivity, diagnostic accuracy, and accuracy of immunohistochemical subtyping to 100%. We recommend the use of elastography to increase the accuracy of the core-needle biopsy.

Acknowledgments

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