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ARAŞTIRMA / RESEARCH

Relationship between strain elastography and histopathological parameters in breast cancer

Meme kanserinde strain elastografi ile histopatolojik parametreler arasındaki ilişki

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Abstract

Purpose: This study aimed to evaluate the relationship between strain elastography and immunohistochemical markers, the histologic grade, and molecular subtyping in invasive breast cancer.

Materials and Methods: The relationships between the elastography index values and progesterone receptor, estrogen receptor, human epidermal growth factor receptor 2, Ki-67, the histologic grade, and molecular subtype in 171 patients who had not received neoadjuvant treatment and underwent breast-conserving surgery were evaluated. Strain elastosonography were used to evaluate elastography index.

Results: The mean patient age was 46.871 ± 11.949 years. There were 135, 129, and 90 estrogen receptor-positive, progesterone receptor-positive, and human epidermal growth factor receptor 2-positive patients, respectively. Forty-seven patients had the worst histological grade. Based on molecular subtyping, human epidermal growth factor receptor 2-positive, luminal A, luminal B, and triple-negative classifications were made for 25 (14.5%), 29 (17.0%), 109 (63.7%), and 8 (4.7%) cases, respectively. There was no statistically significant correlation between the elastography index values and estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, Ki-67, histologic grade, or molecular subtype among these breast resection cases.

Conclusion: The elastography index value was insufficient to predict the specified histopathological parameters.

Keywords:. Sonoelastography, breast, malignancy, histopathology

Öz

Amaç: Bu çalışmanın amacı strain elastografinin invaziv meme kanserinde immünhistokimyasal, histolojik grade ve moleküler subtiplendirmeyle ilişkisini değerlendirmektir

Gereç ve Yöntem: Neadjuvan tedavi almamış meme koruyucu cerrahi geçirmiş 171 hastanın (yaş ortalaması 46.871 ± 11.949 yıl) elastosonografi indeksi değerleri ile progesteron reseptörü, östrojen reseptörü, insan epidermal büyüme faktörü reseptörü 2, Ki-67, histolojik grade ve moleküler subtipi arasındaki ilişki değerlendirildi. Elastografi indeksini değerlendirmek için strain elastosonografisi kullanıldı.

Bulgular: Hastaların yaş ortalaması 46.871 ± 11.949 yıldı. östrojen reseptörü-pozitif, progesteron reseptörü-pozitif ve insan epidermal büyüme faktörü (HER-2)reseptörü 2 pozitif hasta sayısı sırasıyla 135, 129 ve 90 olarak bulundu. 47 hastanın histolojik derecesi en kötüydü. Moleküler alt tiplendirmeye göre 25 (%14,5), 29 (%17,0), 109 (%63,7) ve 8 (%4,7) hasta sırayla HER-2-pozitif, luminal A, luminal B ve triple negatif olarak sınıflandırıldı. Bu meme rezeksiyonu vakaları arasında elastografi indeks değerleri ile östrojen reseptörü, progesteron reseptörü, insan epidermal büyüme faktörü reseptörü 2, Ki-67, histolojik derece veya moleküler alt tip arasında istatistiksel olarak anlamlı bir korelasyon yoktu.

Sonuç:. Elastografi indeksi değeri belirtilen histopatolojik parametreleri ön görmede yetersizdir.

Anahtar kelimeler: Sonoelastografi, meme, malignite, histopatoloji

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INTRODUCTION

Breast screening is routinely performed by mammography. Ultrasonography is used together with mammography as a complementary examination, especially in women with dense breast parenchyma[1,2,3]. In recent years, ultrasonography has been widely used for differentiating malignant and benign solid breast lesions[4]. Studies have shown that elastography increases the diagnostic efficiency of ultrasonography in differentiating between malignant and benign lesions[5,6]. Elastosonographic examination can be easily performed using non-invasive B-mode ultrasonography devices based on the difference in tissue stiffness between the lesion and the adjacent normal parenchyma[4,7]. There are two methods that can be used. Shear wave elastography (SWE) uses an acoustic radiation force impulse, whereas during strain elastosonography (SE), repeated force is applied with a probe by the user[2,8]. Although the methods are different, they have been shown to have similar diagnostic performance for breast lesions[9,10].

The histologic grade, histologic type, tumor size, and presence of lymph node metastasis are prognostic and predictive factors for breast cancers, which are evaluated with biopsies or surgical specimens[11,12]. Moreover, immunohistochemically obtained values of the estrogen receptor (ER), human epidermal growth factor receptor 2 (HER-2), Ki-67 proliferation index, and progesterone receptor (PR) are biomarkers that are used to classify breast cancer subtypes, and these have a role in determining treatment, in addition to being prognostic factors[13,14]. HER-2-positive patients have a poor prognosis and receive specific anti-HER-2 treatment[15]. In addition, hormonal therapy is used to treat ER- and PR-positive patients[16].

Many studies have investigated the relationship between sonoelastography and immunohistochemical biomarkers with prognostic predictive values in breast cancer. However, most of these studies were conducted using SWE. Using SE in the present study, we attempted to examine whether there was a correlation between the immunohistochemical markers, histologic grade, molecular subtyping, and prognosis of patients who underwent breast-conserving surgery without neoadjuvant therapy.

We included patients in the current study who had breast conservation and did not receive adjuvant treatment. The SE method used in the current study is one of the most important features that distinguish it from those previously published. We believe that our original study, which aims to investigate the relationship between SE and histopathological parameters, will make a unique contribution to the literature.

MATERIALS AND METHODS

Ethical approval for this study was obtained from the Adiyaman University Clinical Research Ethics Committee (Approval Date: 21/09/2021, Approval Code: 2021/07-15). Our study was conducted at our tertiary care center, Adıyaman University Training and Research Hospital. Patients who underwent gray-scale ultrasonography and SE before breast Tru-cut biopsy and breast-conserving surgery were included. Written informed consent was obtained from the patients before the procedure, and they were verbally informed. The study was carried out in accordance with the Declaration of Helsinki. Patient information was not shared with third parties at any stage.

Procedure

All evaluations were performed several times for each lesion and were reviewed by the consensus of two radiologists with 11 and 23 years of experience in breast imaging. Patients whose elastosonography index (ESI) values were obtained via SE at our center between March 2018 and September 2021 and who subsequently underwent breast-conserving surgery were included. Patients who received neoadjuvant therapy and were treated surgically with approaches other than breast-conserving therapy were excluded. A total of 195 patients who did not meet the inclusion criteria were excluded.

Inclusion criteria (n: 171) were those with breast-conserving surgery who had no neoadjuvant therapy abd have only single lesion. The exclusion criteria (n: 195) were thos who have not receive breast-conserving surgery, who has receeved neoadjuvant therapy, have multicentric and/or multifocal lesions, mastitis and ductal carcinoma in situ.

Image data acquisition

Masses detected using B-mode ultrasonography were evaluated using the SE mode of a Hitachi Vision Preirus ultrasonography device (Hitachi Medical Systems, Tokyo, Japan). The entire lesion, subcutaneous adipose tissue, adjacent normal breast parenchyma, and pectoral muscle tissue were

included in the images. Mild repetitive pressure was applied to the skin using a transducer mechanically toward the lesion in the vertical direction. Using the obtained elastography images, strain values were determined for the lesion and the adjacent normal breast parenchyma. The ESI values were obtained by calculating the values previously obtained using the device (Figure 1).

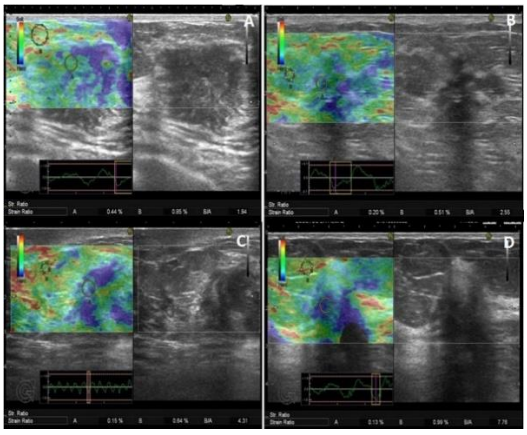

Figure 1. This figure shows the difference in the elastography values of four different lesions classified as Luminal B according to molecular subtyping.

Histopathologic data acquisition

Histological tumor grade was based on the established criteria for nuclear pleomorphism, tubule formation, and mitotic count according to the Nottingham Grading System. A total score was derived from the summation of the three component scores, low-grade (I), intermediate (II), and high-grade (III) tumors.

For immunohistochemical studies, formalin-fixed, paraffin-embedded tissue sections were stained with antibodies for ER, PR, HER2, and Ki-67. ER, PR and HER2 staining of the tumors were evaluated according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. Expression of PR and ER was considered negative when less than 1% of tumor cells were stained. The intensity of nuclear staining, percentage of nuclear staining, and antibodies utilized for PR and ER detection were recorded for all available cases. c-erbB2 expression levels were classified into four groups. HER2 status was deemed positive with a score of +3 and negative with a score of 0 or +1. Tumors with a score of +2 were subjected to dual *in situ* hybridization. This test determines HER2 amplification in the event that the ratio of the HER2 gene signal to the chromosome 17 signal is two or more, which is classified as positive.

Ki-67 was quantified as the percentage of cells that displayed nuclear staining among at least 1000 tumor cells in the high-power field. Ki-67 expression was divided according to percentage levels: <14% and>14%.

The molecular subtypes of breast cancer were stratified by HER2, PR, and ER status and were categorized as follows: luminal type A (ER-and/or PR-positive, HER2 negative), luminal type B (ER-and/or PR-positive, HER2 positive), HER2 positive type (ER- and PR-negative, HER2 positive) and triple-negative type (ER-, PR and HER2 negative).

Statistical analysis

Statistical frequency analysis, mean comparison tests, correlation tests, and chi-squared correlation tests were performed. The Mann-Whitney U test was used for comparisons between two independent groups, and the Kruskal-Wallis H test was used for comparisons between three or more independent groups. Spearman's correlation test was used to determine the direction and severity of the correlation between the numerical measurement scores. When the power analysis is performed, if 150 patients are studied, a test power of about 86% is reached. The sample size used in the study was found to be statistically sufficient as it was over 80%. The margin of error was set at 5% in this study, and the analyses were performed using IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

The 171 patients included in this study were all females. The mean patient age was 46.871 ± 11.949 years. The number of ER-, PR-, and HER-2-positive patients was 135, 129, and 90, respectively. Forty-seven patients had the worst histologic grade, and 36 had the best. In the breast cancer classification performed according to molecular subtyping, HER-2-positive, luminal A, luminal B, and triple-negative classifications were made for 25 (14.5%), 29 (17.0%), 109 (63.7%), and 8 (4.7%) cases, respectively (Table 1).

Table 1. Results of the frequency analysis

Variable	n	%
Sex		
Male	0	0
Female	171	100
Age*	46.871 ± 11.949	
ER		
Negative	36	21.1
Positive	135	78.9
PR		
Negative	42	24.6
Positive	129	75.4
HER-2		
Negative	81	47.4
Positive	90	52.6
Histologic grade		
Worst	47	27.5
Moderate	88	51.5
Best	36	21.1
Molecular subtypes		
HER 2+	25	14.6
Luminal A	29	17.0
Luminal B	109	63.7
Triple -	8	4.7

ER: Estrogen Receptor, PR: Progesterone Receptor, HER: Human Epidermal Growth Factor Receptor, *Mean ± standard deviation

Table 2. Comparison of elastosonography index values by group

Variable	Group	Median	Min	Max	Z	p-value
ER	Negative	3.095	1.460	7.650	-0.368	0.716[M]
	Positive	3.130	1.260	7.650		
PR	Negative	3.280	1.460	7.650	1.416	0.158[M]
	Positive	3.000	1.260	7.650		
HER-2	Negative	3.140	1.260	7.650	-0.476	0.636[M]
	Positive	3.075	1.460	7.650		
Histologic grade	Grade 3	2.740	1.260	5.650	4.332	0.115[K]
	Grade 2	3.280	1.480	7.650		
	Grade 1	2.835	1.460	6.480		
Molecular subtypes	HER 2+	3.140	1.460	7.650	0.640	0.887[K]
	Luminal A	2.860	1.260	7.650		
	Luminal B	3.130	1.460	7.650		
	Triple -	3.160	1.480	6.780		

ER: Estrogen Receptor, PR: Progesterone Receptor, HER: Human Epidermal Growth Factor Receptor, Min: Minimum, Max: Maximum, M: Mann-Whitney U test, K: Kruskal-Wallis H test

Table 3. Correlation between the elastosonography index values and breast resection Ki-67 values

	Mean	SD	1	2	
1. ESI	3.235	1.312	1		
2. Breast resection Ki-67	33.749	21.154	-0.128	1	

SD: Standard deviation

Table 2 shows the results of the Mann-Whitney U test and Kruskal-Wallis H test for ESI values by group. There was no statistically significant correlation between the ESI values and ER, PR,

HER-2, Ki-67, histologic grade, or molecular subtype among the breast resection cases (p>0.05) (Table 2)

Table 3 shows the Spearman correlation test results for the correlation between the ESI values and breast resection Ki-67 values in the individuals participating in the study. There was no statistically significant correlation between the ESI values and breast resection Ki-67 values (r=-0.128, p>0.05) (Table 3).

DISCUSSION

In the present study, there was no significant correlation between the ESI values obtained using SE and the immunohistochemical markers, histologic grade, or molecular subtyping, which are prognostic predictive factors in breast cancer.

Although SE appears to be a user-dependent examination, there was no significant diagnostic difference between SE and SWE[17]. Moreover, although studies have shown a correlation between immunohistochemical markers in breast cancer using SWE, studies using SE are rare. Cho et al. examined the prognostic value of SE. However, they used the Tsukuba elastography scoring system to score findings from one to five and investigated the correlation between immunohistochemical markers and elastosonography[4]. In this study, semiquantitative ESI was used. The present study and the study by Cho et al. revealed that SE results had no significant correlation with the immunohistochemical markers, histological grade, or molecular subtyping of invasive breast cancers[4].

In the study conducted by Kim et al., which showed that the breast tumor strain ratio was a predictive parameter in the demonstration of axillary lymph node metastasis in invasive breast cancers, a method similar to that applied in the present study was used[18]. Similar to the present study, Kim et al. revealed that the strain ratio values were not significantly correlated with ER, PR, HER-2, or the Ki-67 proliferation index[18]. Li et al. showed no significant difference between the strain ratio values in triple-negative and triple-positive breast cancers[19]. Hayashi et al. demonstrated a correlation between elastography and neoadjuvant treatment response using the Tsukuba score. After dividing the lesions into two categories, soft (scores of one, two, and three) and hard (scores of four and five), they revealed a significant correlation between PR and stiffness[20]. The present study showed that there was no correlation between the considered receptors using ESI rather than the Tsukuba score. In a study by Ma et al. using SWE and SE to evaluate the response to neoadjuvant chemotherapy among 71 patients, no significant difference was found[21].

Gemici et al. showed no correlation between the elastography values obtained using SWE and immunohistochemical parameters or molecular subtyping[22]. In the same study, it was shown that there were significant correlations between SWE stiffness rates and lymphovascular invasion, lymph node metastasis, and histological grade. In the study by Kim et al., it was observed that lesions with negative PR and high Ki-67 proliferation index had high stiffness rates, as obtained with SWE[23]. Similarly, Gu et al. showed significant correlations between lymph node metastasis, histological grade, and SWE stiffness rates. In the same study, immunohistochemical parameters and SWE showed that lesion stiffness was more pronounced in progesterone-, estrogen-, and HER-2-positive patients and those with high Ki-67 proliferation index values[12]. Song et al. showed significant correlations between high stiffness rates obtained by SWE, lymph node metastasis, and lymphovascular invasion. However, they showed no significant correlation between PR, ER, HER-2, or Ki-67 proliferation index and SWE stiffness rates. Similarly, other studies have shown a significant correlation between lymph node metastasis, histologic grade, lymphovascular invasion, and sonoelastographic results, but different results for immunohistochemical parameters and sonoelastography have been obtained[12,22,23].

The present study had several limitations. The retrospective nature of the study and the fact that it was conducted in a single center might have inevitably led to bias in case selection. Furthermore, the immunohistochemical parameter evaluations were performed only in terms of histologic grade and molecular subtyping; therefore, correlations between other prognostic factors and ESI were not evaluated. In addition, the examinations were performed only with an ultrasonography device, no comparisons were performed of variations with other devices, and the examinations were conducted at a single time point and were not repeated. Therefore, prospective studies with larger sample sizes are required to confirm our findings. Nevertheless, this study has several strengths. The examinations were conducted with the consensus of two radiologists experienced in breast radiology, and the evaluations were repeated to obtain the ESI values. Another strength is that the

lesions included in the analysis were of sizes that made elastosonography optimal, and the study population consisted of patients who had undergone breast-conserving surgery.

In conclusion, the correlations between the ESI values obtained using SE and the immunohistochemical markers of histopathological examination, histologic grade, and molecular subtyping in patients with invasive breast cancer who had not received neoadjuvant treatment and underwent breast-conserving surgery were examined. We found that there was no significant correlation between the ESI values and the features of histopathological evaluation showing prognosis. To achieve better results in predicting the prognosis of patients with breast cancer, further studies need to be conducted with a larger sample and using different methods.

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