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ARAŞTIRMA / RESEARCH

Histogram analysis for the differentiation of malignant and benign lesions in breast magnetic resonance imaging: preliminary study

Meme manyetik rezonans görüntülemede malign ve benign lezyonların ayrımında histogram analizi: ön çalışma

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Abstract

Purpose: The present study assesses whether malignant and benign lesions can be distinguished through histogram analysis of non-fat-suppressed T1-weighted and fat-suppressed T2-weighted breast magnetic resonance images (MRIs).

Materials and Methods: MRIs of 20 malignant and 20 benign breast lesions were reviewed retrospectively by histogram analysis performed using Osirix V.4.9 software. The regions of interest (ROIs) were drawn manually to include almost the entire lesion, and values from these ROIs were used to calculate gray-level intensity mean, standard deviation, entropy, uniformity, skewness, kurtosis, and percentile values.

Results: In non-fat-suppressed T1-weighted images, the minimum, 1st, 3rd, 5th, 10th and 25th percentile values were significantly lower in the malignant lesions than in the benign lesions. The minimum value had sensitivity of 70% and specificity of 63.2%. On the fat-suppressed T2-weighted images, skewness was significantly higher while uniformity was significantly lower in malignant lesions than benign lesions. Skewness had 68.4% sensitivity and 60% specificity, and uniformity had 65% sensitivity and 68.4% specificity.

Conclusion: The results of this study demonstrated that histogram analysis of non-fat-suppressed T1-weighted and fat-suppressed T2-weighted images can be used to differentiate malignant and benign lesions in breast MRI.

Keywords:. Breast, malignant, benign, magnetic resonance imaging, histogram

Öz

Amaç: Bu çalışma, yağ baskısız T1 ağırlıklı ve yağ baskılı T2 ağırlıklı meme manyetik rezonans (MR) görüntülerinin histogram analizi ile malign ve benign lezyonların ayırt edilip edilemeyeceğini incelemeyi amaçladı.

Gereç ve Yöntem: 20 malign, 20 benign hastanın MR görüntüleri retrospektif tarandı. Görüntülerin histogram analizi için Osirix V.4.9 yazılımı kullanıldı. İlgi alanları (ROI) elle lezyonun tamamına yakınını kapsayacak şekilde çizildi. ROI değerlerinden gri seviye yoğunluğu, ortalama, standart sapma, entropi, tekdüzelik, çarpıklık, basıklık, boyut % alt, boyut % üst, boyut % ortalama hesaplandı. Tüm görüntü analizi MATLAB'da kurum içi program kullanılarak sağlandı.

Bulgular: Yağ baskısız T1 ağırlıklı görüntülerde, Minimum, %1, %3, %5, %10 ve %25'inci değerleri; malign lezyonlarda benign lezyonlara göre istatistiksel anlamlı olarak daha düşük izlendi. Minimum değer için sensitivite %70, spesifite %63.2 olarak saptandı. Yağ baskılı T2 ağırlıklı görüntülerde Skewness değeri malign lezyonlarda benign lezyonlara göre istatistiksel anlamlı olarak daha yüksek, Uniformity değeri; malign lezyonlarda benign lezyonlara göre istatistiksel anlamlı olarak daha düşük izlendi. Skewness değer için sensitivite %68.4, spesifite %60 olarak saptandı. Uniformity değer için sensitivite %65, spesifite %68.4 olarak saptandı.

Sonuç: Bu çalışma, yağ baskısız T1 ağırlıklı ve yağ baskılı T2 ağırlıklı görüntülerin histogram analizinin meme MR görüntülemede malign ve benign lezyonları ayırt etmek için kullanılabileceğini göstermektedir.

Anahtar kelimeler: Meme, malign, benign, manyetik rezonans görüntüleme, histogram

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INTRODUCTION

Breast cancer is the most common form of cancer among women, accounting for 15% of cancer-related mortalities[1,2]. Breast cancer morbidity and mortality can be reduced with early diagnosis, for which the current approach is annual breast cancer screening with mammography in women starting at the age of 40[3]. Women with an estimated lifetime breast cancer risk of 20%-25% or higher are classified as high-risk. For this group, the American Cancer Society recommends breast magnetic resonance imaging (MRI) along with mammography for breast cancer screening[4]. Breast MRI offers the highest sensitivity among the available clinical imaging methods, detecting 90% of malignant tumors. However, it has a relatively low specificity of 72%[5]. For this reason, differentiating between malignant and benign lesions detected on MRI can still be challenging[6].

Histogram analysis of images can reveal the quantitative texture-based features of tissue by measuring signal heterogeneity that cannot be visually perceived by the human eye[7]. A gray-level intensity histogram provides a concise and simple summary of the statistical data present in the image. The calculation of gray-level histograms is based on individual pixels, providing first-degree statistical information about the image[8]. This information includes the average gray-level intensity (mean), standard deviation of the histogram (standard deviation), entropy, skewness, minimum, median, and maximum intensity values, variance, uniformity, kurtosis, size %lower, size %mean, size %upper, and percentile values, as previously described[9,10]. This approach allows images to be analyzed more objectively and provides more reliable information for the identification and classification of benign and malignant tumors[11]. Studies are currently being conducted to clarify the benefit of histogram analyses in the diagnosis and treatment follow-up of tumoral lesions. A previous study reported that besides demonstrating tumor heterogeneity, histogram analyses can be used to differentiate between benignity and malignancy, identify the level of aggressiveness, and predict treatment response[12].

The differential diagnosis of any lesion from breast MRI is based on the morphology and perfusion kinetics of the lesion and a comparison of signals on T1- and T2-weighted images[13]. Clinically, non-fat-suppressed T1-weighted images are better for visualizing normal anatomical structures, whereas pathological signal changes are best recognized on T2-weighted images[14, 15]. Given these features, we think both non-fat-suppressed T1-weighted and fat-suppressed T2-weighted images are important when performing tissue analysis. In the literature, diffusion and contrast-enhanced sequences have been assessed in several MRI histogram analysis studies on the differentiation of malignant and benign breast lesions. However, the contrast signal is dominant in contrast-enhanced sequences, and we believe that sequence analyses that reflect the native tissue signal provide more valuable information in tissue analysis. The aim of this preliminary study was to investigate the diagnostic efficiency of histogram analysis of non-fat-suppressed T1-weighted and fat-suppressed T2-weighted sequence images reflecting the natural tissue signal in the differential diagnosis of benign and malignant breast lesions. To the best of our knowledge, this is the first study to use histogram analyses of non-fat-suppressed T1-weighted and fat-suppressed T2-weighted breast MRI to distinguish malignant and benign lesions.

MATERIALS AND METHODS

This retrospective study was approved by the local ethics committee of Fırat University (date: 31/12/2020; approval number: 2020/17-26). As the study was retrospective in nature, informed consent was not required.

Patients

Of 111 patients who underwent MRI in the radiology department of Fırat University Hospital in 2019 and 2020, 66 women with a histopathological diagnosis were enrolled. Twenty six patients who underwent surgery, medical treatment, or interventional procedures before imaging or whose images were not suitable for analysis were excluded. As a result, a total of 40 female patients, 20 with malignant and 20 benign diagnoses, were included in the study. Twenty eight of the patients were postmenopausal and 12 were premenopausal.

MRI technique

Breast imaging was performed using a 1.5-Tesla MRI scanner (GE, Milwaukee, Wisconsin, USA) with a 7-channel breast coil. The patients were placed in prone position with their breasts inside the coils, and light pressure was applied with pressure pads to reduce motion artifacts. The bilateral breast imaging

technique was used. Breast MRI was performed between days 7 and 14 of the menstrual cycle in premenopausal patients to avoid lesion masking by fibroglandular tissue and reduce false positives. Following the acquisition of localizer and calibration images in the axial, coronal and sagittal planes, T2 IDEAL (TR: 9300 ms, TE: 102 ms, FOV: 380 x 380 mm, Matrix: 352 x 288, NEX: 1, slice thickness: 3 mm), 3D T1 VIBRANT (TR: 5.4 ms, TE: 2.6 ms, FOV: 380 x 380 mm, Matrix: 416 x 320, slice thickness: 1.4 mm), and fat-suppressed T2 (TR: 7326 ms, TE: 85 ms, FOV: 380 x 380 mm, Matrix: 224 x 224, NEX: 2, slice thickness: 3 mm) images were acquired. After obtaining the fat-suppressed 3D T1-weighted VIBRANT sequence (TR: 4.6 ms, TE: 2.1 ms, FOV: 380 x 380 mm, Matrix: 320 x 320, slice thickness: 1.6 mm), an automatic injector was used to administer contrast agent containing gadoteric acid or gadobutrol via the antecubital vein at a dose of 0.1 mmol/kg and a flow rate of 2 ml/s, followed by the injection of 20 ml normal saline. Immediately after saline injection, dynamic postcontrast images were acquired using the same parameters used for the precontrast T1-weighted images.

Image analysis

Images were obtained from the picture archiving and communication system (PACS) and uploaded to a 27-inch iMac computer (Apple Inc., Cupertino, CA, USA). OsiriX V.4.9 imaging software (Pixmeo, Switzerland) was used for histogram analysis of the region of interest (ROI). The images were assessed by two radiologists with 10 (S.A., Rater 1) and 20 (M.B., Rater 2) years of experience. Rater 1 manually defined the ROI for each lesion. Rater 2 checked the ROI settings. The raters resolved any disagreement about the lesion boundaries by discussing between themselves. In dynamic images, the ROI was traced on the lesion in the section with the most intense contrast enhancement and largest lesion dimensions. The ROI on the contrast-enhanced images was matched with the T1- and T2-weighted images (Figure 1).

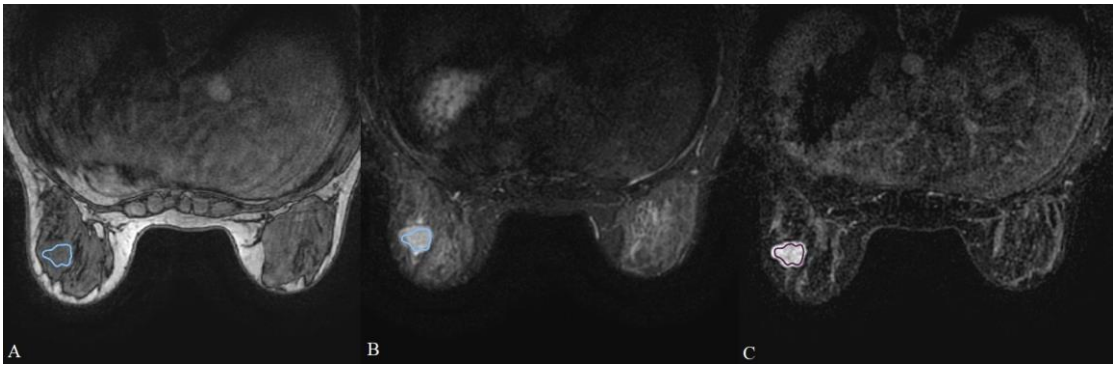

Figure 1. MR images of a patient with fibroadenoma and the regions of interest used for analysis A) Non-fat-suppressed T1-weighted images, B) Fat-suppressed T2-weighted images, C) Postcontrast fat-suppressed T1-weighted images.

The ROI size was selected to include as much of the analyzed lesion as possible to avoid partial volume effect and to obtain an adequate pixel number. The gray-level intensity values obtained from the ROI were used to calculate the mean and standard deviation of the histogram and entropy, skewness, uniformity, kurtosis, percentile, and size %upper, size %lower, size %mean (%U, %L and %M) values. The image analysis algorithm was created using an in-house program written in MATLAB (version R2017a; MathWorks, Natick, MA, USA).

Statistical analysis

IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp.) was used for the statistical analysis. The normality of the data distribution was assessed with a Kolmogorov–Smirnov test. Based on the results, the data were summarized using mean ± standard deviation and group comparisons were performed with Student's t-test and Mann-Whitney U test. A value of $p<0.05$ was considered statistically

significant. Receiver operating characteristic (ROC) curve analysis was performed for selected variables found to differ significantly between malignant and benign lesions. PASS 11 software (PASS 11. NCSS, LLC. Kaysville, Utah, USA) was used for post hoc power analysis.

RESULTS

A total of 20 benign and 20 malignant lesions were included in the study. Among the malignant lesions were 4 ductal carcinomas in situ (DCIS), 15 invasive ductal carcinomas, and 1 invasive lobular carcinoma, while the benign lesions included 13 fibroadenomas, 2 granulomatous lesions, 1 adenosis, and 4 intraductal papillomas (Table 1).

The mean ages of the patients in the benign and malignant group were 45.30±11.95 and 49.90±9.13, respectively (p = 0.179). There was no significant difference in the side (right/left breast) (p = 0.527), quadrant (p=0.370), or size (p = 0.285) of the tumors between the benign and malignant groups (Table 2).

In the non-fat-suppressed T1-weighted images, the minimum, 1st, 3rd, 5th, 10th, and 25th percentile values were significantly lower in malignant lesions than benign lesions (Table 3).

Table 1. Distribution of malignant and benign lesions

	N	%
Benign	20	100
Fibroadenoma	13	65
İntraductal Papilloma	4	20
Granulomatous Mastitis	2	10
Adenosis	1	5
Malign	20	100
Invasive Ductal Carcinoma	15	75
Ductal Carcinoma In Situ	4	20
Invasive Lobular Carcinoma	1	5

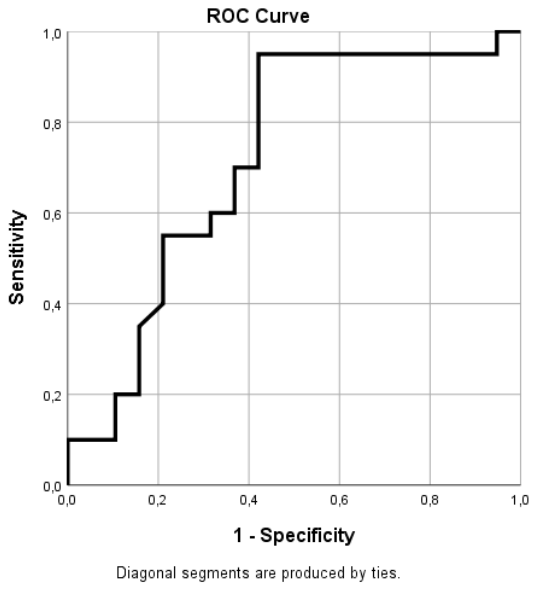

Figure 2. ROC analysis for minimum value on non-fat-suppressed T1-weighted images

ROC curve analysis of minimum value yielded an area under the curve (AUC) of 0.720 (confidence interval [CI]: 0.551-0.888). At a cut-off value of 202.5, the two groups could be differentiated with 70% sensitivity and 63.2% specificity (Figure 2).

On the fat-suppressed T2-weighted images, skewness was significantly higher while uniformity was significantly lower in the malignant lesions than the benign lesions (Table 4). In the ROC curve analysis of skewness, AUC was 0.692 (CI: 0.524-0.860). At a cut-off value of -0.0376, the two groups could be differentiated with 68.4% sensitivity and 60% specificity (Figure 3).

ROC curve analysis of uniformity gave an AUC of 0.716 (CI: 0.552-0.879). A cut-off value of 0.3111, the two groups could be differentiated with 65% sensitivity and 68.4% specificity (Figure 4).

At the 0.05 significance level (alpha), the power to detect differences between groups for different parameters was between 80-100%.

Table 2. The mean diameter of the benign and malignant lesions and the mean age of the patients

	Benign (20)		Malign (20)		p
	Mean	**Std. Deviation**	**Mean**	**Std. Deviation**	**Student t**
Age	45.30	11.95	49.90	9.13	0.179
Diameter (mm)	20.55	7.07	24.05	12.60	0.285

*Student's t

Table 3. Histogram parameters of non-fat-suppressed T1- weighted images in benign and malignant breast lesions

T1 Weighted	Benign (20)		Malign (20)		p	
	Mean	**Std. Deviation**	**Mean**	**Std. Deviation**	**Student t**	**Mann-Whitney U**
Mean	740.14	202.95	604.79	197.91		0.129
Standard Deviation	141.14	85.66	159.32	86.74		0.415
Minimum	333.40	199.20	191.47	209.61		0.019
Maximum	1055.55	318.05	1097.58	374.08		0.933
Median	752.18	212.57	604.45	208.46		0.109
Variance	26892.45	36850.98	32510.88	35502.07		0.415
Entropy	6.33	0.70	6.41	0.60	0.719	
Size%L	15.42	3.31	14.55	5.31	0.538	
Size%U	13.96	4.00	14.17	3.94		0.800
Size%M	70.62	6.74	71.28	8.64	0.790	
Kurtosis	3.99	2.52	5.96	8.74		0.613
Skewness	-0.41	0.73	0.08	1.49		0.312
Uniformity	0.35	0.11	0.29	0.15	0.120	
Percent01	382.08	186.06	235.68	195.78	0.022	
Percent03	447.70	160.82	308.27	186.34	0.017	
Percent05	494.85	158.25	346.09	184.71	0.010	
Percent10	552.88	170.29	409.50	186.61	0.017	
Percent25	651.91	195.01	502.04	192.69		0.046
Percent75	839.15	243.31	706.08	226.00	0.085	
Percent90	902.78	268.41	791.81	252.76	0.192	
Percent95	944.75	289.10	853.56	280.92		0.613
Percent97	970.50	301.11	906.00	304.95		0.757
Percent99	1017.95	314.15	1007.84	362.60		0.757

*Student's t, **Mann-Whitney U.

Table 4. Histogram parameters of fat-suppressed T2- weighted images in benign and malignant breast lesions

T2 Weighted	Benign (20)		Malign (20)		p	
	Mean	Std. Deviation	Mean	Std. Deviation	Student t	Mann-Whitney U
Mean	512.32	258.40	399.14	139.14	0.099	
Standard Deviation	92.95	36.77	86.05	30.80	0.531	
Minimum	254.85	180.23	195.16	119.01	0.233	
Maximum	741.05	316.58	690.53	265.45	0.593	
Median	515.28	268.59	392.92	137.95	0.084	
Variance	9923.13	7231.50	8303.31	5097.45	0.426	
Entropy	6.49	0.66	6.46	0.55	0.860	
Size%L	15.84	3.39	14.59	3.59	0.271	
Size%U	15.28	4.39	15.09	3.61	0.887	
Size%M	68.88	5.23	70.32	6.47	0.450	
Kurtosis	3.47	1.89	4.03	2.18		0.068
Skewness	***-0.14***	***0.69***	***0.40***	***0.82***	***0.032***	
Uniformity	***0.33***	***0.11***	***0.24***	***0.11***	***0.020***	
Percent01	294.99	183.26	222.69	120.89	0.157	
Percent03	334.69	197.06	254.05	128.54	0.141	
Percent05	361.16	210.96	269.22	127.48	0.110	
Percent10	394.01	225.42	298.15	131.20	0.116	
Percent25	450.36	248.28	342.17	134.81	0.102	
Percent75	576.61	273.57	451.17	144.93	0.084	
Percent90	629.34	284.63	505.59	155.85	0.103	
Percent95	658.11	291.50	544.52	173.32	0.150	
Percent97	679.60	300.83	573.68	190.59		0.339
Percent99	709.89	308.91	626.69	217.56	0.339	

*Student's t, **Mann-Whitney U

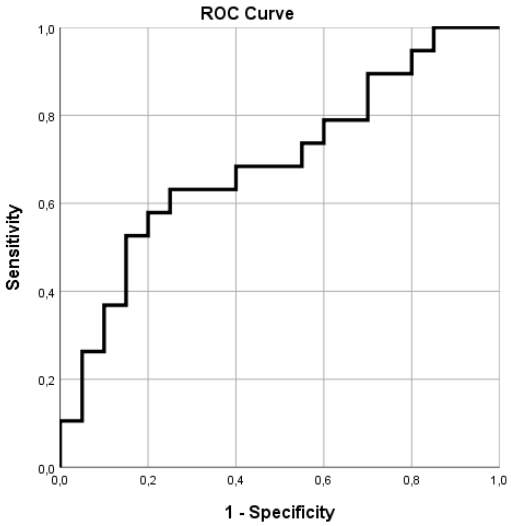

Figure 3. ROC analysis of skewness on fat-suppressed T2-weighted images

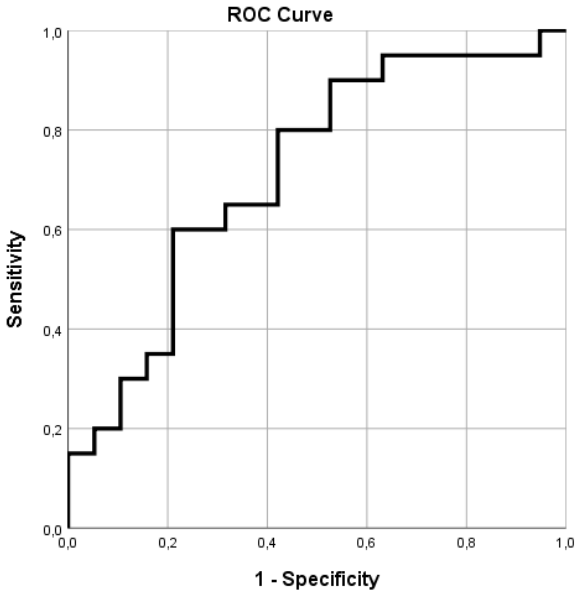

Figure 4. ROC analysis of uniformity on fat-suppressed T2-weighted images.

DISCUSSION

MRI is the most sensitive imaging technique for the detection of breast cancer, but due to its low specificity, it is generally used together with ultrasonography and mammography. MRI provides information about both the dynamic (contrast enhancement pattern and type) and morphological features (size, shape, and margin features) of lesions[16]. The main benefit of MRI in the differentiation of malignant and benign lesions is its potential to reduce the number of biopsies for benign lesions; therefore, it is desirable to obtain the highest possible negative predictive value in breast MRI. With histogram analysis, indistinguishable features of the tissue can be distinguished using numerical data, thereby increasing the success of diagnostic radiology[17]. Our review of the literature revealed that previous studies on the differentiation of malignant and benign breast lesions were based on the analysis of contrast-enhanced and diffusion sequence images. In contrast, we analyzed non-fat-suppressed T1- and fat-suppressed T2-weighted images in the present study. T1-weighted sequences provide excellent spatial resolution and soft-tissue contrast, thereby enabling anatomical examination, whereas T2-weighted sequences better demonstrate pathological changes in signal intensity[18]. Contrast-enhanced sequences are dominated by the contrast signal in the lesion. As non-contrast, non-fat-suppressed T1-and fat-suppressed T2-weighted sequence images reflect the natural tissue signal, we believe tissue analyses using these sequences may be more valuable.

A previous study reported significant differences in the texture characteristics of benign and malignant breast lesions in tissue analysis of postcontrast T1-weighted MRI images. Variance, total entropy, and entropy were identified as the most significant factors differentiating benign and malignant lesions[19]. A meta-analysis showed that apparent diffusion coefficient (ADC) histogram analysis has 85% sensitivity and 79% specificity in the accurate differentiation of malignant and benign breast lesions, as well as a good diagnostic performance. The same meta-analysis concluded that the 50th percentile had the greatest accuracy among histogram parameters [20].

A number of earlier studies involving breast MRI postcontrast T1-weighted images and diffusion histogram analyses have identified percentile values as the most significant parameters in the differentiation of benign and malignant lesions, although there is a lack of consensus on which

percentile is most accurate. Some studies have reported the 10th percentile value had a sensitivity of 82.35–94.1% and a specificity of 84.1–100% in differentiating malignant and benign lesions, while others have stated that the minimum and 25th percentile values were the most significant parameters[21,22,23,24]. In the present study, the minimum and 1st, 3rd, 5th, 10th, and 25th percentile values on non-fat-suppressed T1-weighted images and skewness and uniformity values on fat-suppressed T2-weighted images were identified as the most significant parameters in differentiating between malignant and benign lesions.

A tissue analysis study evaluating invasive breast cancer heterogeneity revealed significant differences in uniformity and entropy on T2- and postcontrast T1-weighted subtraction images. On postcontrast T1-weighted subtraction images, high-grade tumors exhibited greater uniformity and lower entropy values, while on T2-weighted images, higher grades were associated with decreased uniformity and increased entropy. Breast cancer patients with greater heterogeneity on T2-weighted images (higher entropy) and less heterogeneity on contrast-enhanced T1-weighted subtraction images (low entropy) exhibited poorer recurrence-free survival[25,26]. It was also observed in the present study that uniformity was significantly lower and skewness was significantly higher in malignant lesions than in benign lesions on T2-weighted images.

Our study has certain limitations. First, the sample size was small and included only a few types of breast lesions. Most benign lesions were fibroadenoma, and most malignant lesions were invasive ductal carcinoma. In addition, all breast lesions included in the study were larger than 1 cm. These factors may lead to sample selection bias. Furthermore, all study parameters were calculated from manually drawn ROIs rather than a standard ROI.

This study showed that histogram analysis of lesions on breast MRI can be used to differentiate benign and malignant lesions. However, there are different results in the literature regarding which histogram parameters are more meaningful in this distinction. To the best of our knowledge, this is the first study to investigate the performance of histogram parameters obtained from non-fat-suppressed T1-weighted and fat-suppressed T2- weighted images in the differentiation of malignant and benign breast lesions. We believe that histogram analysis results from different sequences will provide insight on which parameter is more significant for this purpose. Larger sample sizes and more comprehensive analysis are needed in future studies.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SA, MB; Veri toplama: SA, MB; Veri analizi ve yorumlama: SA, MB; Yazı taslağı: SA; İçeriğin eleştirel incelenmesi: SA, MB; Son onay ve sorumluluk: SA, MB; Teknik ve malzeme desteği: SA, MB; Süpervizyon: SA; Fon sağlama (mevcut ise): yok.
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Ethical Approval: For this study, ethical approval was obtained from the Ethics Committee of Firat University for Non-Interventional Research by its decision dated 31.12.2020 and numbered 2020/17-26.
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