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DAHİLİ TIP BİLİMLERİ/ *MEDICAL SCIENCES*
Araştırma Makalesi/Research Article

Analysis of Morphological Features and Contrast Enhancement Kinetics of Malignant Breast Masses by Magnetic Resonance Imaging

Malign Meme Kitlelerinin Morfolojik Özelliklerinin ve Kontrastlanma Kinetiğinin Manyetik Rezonans Görüntüleme ile Analizi

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Amaç: Mamografide ve ultrasonografide malignite kriterlerini karşılayan meme lezyonlarını dinamik kontrastlı manyetik rezonans görüntüleme (MRG) ile analiz etmeyi amaçladık.

Gereç ve yöntemler: Mamografide ve ultrasonografide malignite bulguları saptanan, yaş ortalaması ± SD, 50,79 ± 11,1 olan 50 kadın olgu çalışmaya alındı ve 51 meme kitlesi 1,5 Tesla gücünde MRG cihazı ile değerlendirildi. T2 ağırlıklı turbo inversion recovery magnitude, kontrast öncesi T1 ağırlıklı SE ve üç boyutlu T1 ağırlıklı Fast Low Angle Shot görüntüler elde edildi. İntravenöz Gadopentenate diethylene tri-amine pentaacetic acid enjeksiyonunu takiben yağ baskılı T1 ağırlıklı 3D fast low angle shot sekansı uygulandı. Lezyonlar morfolojilerine ve kontrastlanma kinetiğine göre kalitatif ve kantitatif olarak değerlendirildi.

Bulgular: Lezyonların ortalama çapı ± SD, 29,15 ± 11,5 mm idi. MRG'de 18 lezyonun konturları spiküle, 26 lezyonun konturları düzensiz, beş lezyonun konturları lobüle ve iki lezyonun konturları düzenli idi. Histopatolojik olarak, 36 lezyon (%70,6) invaziv duktal karsinom, yedi lezyon (%13,7) invaziv lobüler karsinom, üç lezyon (%5,9) invaziv tübüler karsinom, üç lezyon (%5,9) enflamatuar karsinom ve iki lezyon (%3,9) müsinöz karsinom tanısı aldı. Maligniteyi temsil eden tip 3 zaman-sinyal eğrisi ve %80'in üzerindeki erken dönem kontrastlanma hızı (yüzdesi), sırasıyla 35/51 adet (%68,6) ve 39/51 adet (%76,5) meme lezyonunda saptandı. Benigniteyi temsil eden tip 1 zaman-sinyal eğrisi ve %60 veya altındaki erken dönem kontrastlanma hızı (yüzdesi), sırasıyla 1/51 adet (%2) ve 3/51 adet (%5,9) meme lezyonunda saptandı.

Sonuç: Mamografi ve ultrasonografi ile birlikte kullanılan dinamik kontrastlı MRG, malign meme lezyonlarının tanısında yararlı bir yöntemdir.

Anahtar sözcükler: ***Meme, karsinom, manyetik rezonans görüntüleme, kontrast madde***

Aim: Our aim was to analyze breast lesions meeting the malignancy criteria on mammography and breast ultrasonography (US), by using dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI).

Material and Methods: Fifty females with findings of malignancy on mammography and US, with a mean age ± SD of 50.79 ± 11.1 years were included. 51 breast lesions were evaluated using a 1.5 T magnetic resonance imaging system. T2-weighted turbo inversion recovery magnitude, precontrast T1-weighted SE and 3D T1-weighted Fast Low Angle Shot images were obtained. Postcontrast 3D T1-weighted fast low angle shot sequence with fat suppression was applied after intravenous administration of Gadopentenate diethylene tri-amine pentaacetic acid. Lesions were evaluated qualitatively and quantitatively according to their morphology and contrast enhancement kinetics.

Results: Mean size ± SD of the lesions was 29.15 ± 11.5 mm. On MRI, 18 lesions had spiculated contours, 26 had irregular contours, five had lobular contours and two had regular contours. Of 51 breast lesions, 36 (70.6%) were histopathologically diagnosed as invasive ductal carcinoma, seven (13.7%) as invasive lobular carcinoma, three (5.9%) as invasive tubular carcinoma, three (5.9%) as inflammatory carcinoma and two (3.9%) as mucinous carcinoma. Indicating malignancy, type 3 time-signal intensity curve and early-phase contrast enhancement rate more than 80%, were detected in 35/51 (68.6%) and 39/51 (76.5%) breast lesions, respectively. Indicating benignity, type 1 time-signal intensity curve and early-phase contrast enhancement rate equal to or less than 60%, were detected in 1/51 (2%) and 3/51 (5.9%) breast lesions, respectively.

Conclusion: Used with mammography and US, dynamic contrast-enhanced magnetic resonance imaging is a useful method in diagnosis of malignant breast lesions.

Key words: ***Breast, carcinoma, magnetic resonance imaging, contrast media***

Breast cancer is a frequently diagnosed disease in women, and it is the second most frequent reason for deaths in women in developed countries (1). Its incidence is between 0.15–0.45% in women (2). For one out of nine women, there is a probability of having breast cancer in a later period of their life (1). Therefore, screening of breast lesions for early diagnosis, besides diagnosing and evaluating the

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existing lesions are critical for treatment.

The most commonly used method in screening and diagnosing breast lesions in women is X-ray mammography. It has been used successfully in determination and characterization of microcalcifications in breasts. However, it is difficult to differentiate lesions in dense breasts since sensitivity of the mammography method in dense breast parenchyma decreases to as low as 48% (3). Breast ultrasonography (US) is used in combination with mammography.

Breast US may play important role in evaluation of suspicious lesions with irregular borders and in characterization of them. However, US has limitations due to the fact that it is insufficient in showing microcalcifications which have an important role in early diagnosis of breast lesions. Being a user-dependent method is another limitation. Additional imaging methods which could be used together with and in addition to mammography and US have emerged (3, 4). In recent years there has been an increasing interest in magnetic resonance imaging (MRI) as a non-invasive diagnostic modality for further characterization of suspicious breast lesions detected by means of mammography or US. Using US, mammography and MRI together, result in a higher diagnostic sensitivity and negative predictive value as compared to using these modalities individually (5). The aim of this study was to analyze breast lesions which show features of malignancy on mammography and US, with respect to their morphological features and contrast enhancement kinetics by using dynamic contrast-enhanced (DCE) MRI, and to evaluate the MRI results in concordance with the histopathological diagnoses.

Material and methods

In the present study, 50 female patients with findings of malignancy on mammography and US, with a mean age ± SD of 50.79 ± 11.1 years (age range, 27–70 years) were included. Of these patients, 51 lesions were evaluated. This study was performed according to the World Medical Association Declaration of Helsinki. Patients were admitted to MRI unit following clinical examination. Examination of both breasts was done by taking bilateral craniocaudal and mediolateral oblique mammograms with a mammography device (Fischer imaging, HFX plus, Colorado, USA). After MG, breast US examination was performed by using 11 MHz linear transducer (Power Vision 6000, Toshiba Medical Systems, Tokyo, Japan). MRI of both breasts, thoracic wall and axillas was performed with use of a 1.5 T system (Magnetom Vision plus, Siemens Medical system, Erlangen, Germany) by using a breast coil. Motions and breathing artifacts were minimized by positioning the patient in prone position.

We started breast MRI by taking scout images. Scout images consisted of T1-weighted Fast Low Angle Shot (FLASH) sequence (TR/TE/FA: 40/6/140 msec, slice thickness: 10 mm) in all three planes (axial, coronal and sagittal). Following that, T2-weighted turbo inversion recovery magnitude sequence (TIRM) (TR/TE: 9128/60 msec, TI: 150 msec, slice thickness: 3mm) with fat suppression was applied. Field of view was 330x330 mm in all sequences. Precontrast axial T1-weighted spin-echo (SE) sequence (TR/TE: 616/12 msec, slice thickness: 3 mm) and three dimensional (3D) T1-weighted in FLASH sequence (TR/TE: 8.1/4 msec, FA: 20°, slice thickness: 2.5–3 mm) in axial plane was performed. Postcontrast 3D T1-weighted FLASH sequence was acquired after administration of 0.1 mmol/kg bodyweight of gadopentenate diethylene tri-amine pentaacetic acid (Gd-DTPA) (Magnevist; Schering, Berlin, Germany). Gd-DTPA was administered manually in bolus form through a 21G needle-cannula positioned in an antecubital vein. Immediately after the contrast agent, 20 ml isotonic saline solution was injected. Total time of injection was 10 seconds. In the last 10 seconds of the DCE MRI, second examination was applied with nine successive sequences. In order to show the contrasted lesion more accurately and to saturate the fatty tissue, subtracted images were obtained, by subtracting images of first examination from the images of seventh examination. Evaluations were performed directly at the system console by using the automated software available. Images from DCE MRI were interpreted using clinical data and were compared with the findings from conventional mammography and breast US. On DCE MRI, cross-sections in which lesions showed the most prominent contrast enhancement with greatest volumes were chosen for the enhancement kinetics analysis. Region of interests ROIs were between 0.2 and 2.4 cm^2 and were placed to the periphery of the contrast-enhanced lesion. Special care was taken so that there was no motion artifact in images while drawing the time-signal intensity curve for the contrast enhancement kinetics analysis. Besides morphological features of

the lesion, the amount and speed of contrast enhancement were also evaluated and the results of other diagnostic methods were taken into account. Image processing and interpretation were done by two experienced radiologist. Firstly, morphological features of the lesions were determined (size, signal, contour features). Secondly, contrast enhancement kinetic analysis was done qualitatively and quantitatively. The relative enhancement (percentage of signal intensity increase) was calculated quantitatively by using post signal intensity (SI)-pre SI / pre SI x 100 formula. After administration of the contrast agent, if early-phase (first minute) enhancement rate was less than or equal to 60%, it was accepted as benign. If it was more than 60% and less than or equal to 80%, it was accepted as probably malignant. Finally, if it was more than 80%, it was accepted as malignant. After that, interval period and late stage of contrast enhancement as time-signal intensity curve were evaluated visually. According to the shape of the time-signal intensity curve, type 1 (continous, steady enhancement with straight shape) time course (curve pattern) was accepted to indicate benignity. Lesions with type 2 time course (plateau of signal intensity with a sharp bend after the initial upstroke) was accepted as probably malignant, and type 3 time course (wash-out of signal intensity in which there is an initial upstroke, after which enhancement is abruptly cut off, and the signal intensity decreases) was accepted to indicate malignancy. After imaging of the breast lesions, histopathological diagnosis was made through biopsy. One to three weeks after histopathological diagnosis, radical modified mastectomy was performed for all breast lesions.

Results

Of 51 breast lesions, 24 (47.1%) were in the right breast, and 27 (52.9%) were in the left breast (Table 1). One patient had two-sided malignant breast lesions. Mean size ± SD of the lesions was 29.15 ± 11.5 mm (range, 12–70 mm). On mammography, pleomorphic calcifications were shown in 21 lesions (Figure 1) while a few, indeterminate calcifications were observed in four lesions. On mammography of 26 lesions, pathological calcification was not observed. On US, 48 lesions showed irregular contours, whereas three lesions showed lobular contours. On MRI, 18 lesions had spiculated contours, 26 had irregular contours, five had lobular contours and two had regular contours. All of the 51 breast lesions which were determined to meet the malignancy criteria on mammography and US, were histopathologically malignant. Of 51 breast lesions, 36 (70.6%) were histopathologically diagnosed as invasive ductal carcinoma (Figures. 1, 2), seven (13.7%) as invasive lobular carcinoma, three (5.9%) as invasive tubular carcinoma, three (5.9%) as inflammatory carcinoma and two (3.9%) as mucinous carcinoma

Tablo1 : The distribution of qualitative and quantitative MRI evaluation results of malignant breast lesions according to their hystopathologic types

	Time-signal intensity curve			Early period contrast enhancement rate (%)			Internal characteristics of contrast enhancement		Degree of contrast enhancement			Feature of contrast enhancement		
	Type 1	Type 2	Type 3	<60–60	>60–80	>80	Homogeneous	Heterogeneous	Weak	Moderate	Intense	Other	Centrifugal	Centripetal
Invasive ductal carcinoma (n=36)	1	11	24	2	7	27	3	33	3	20	13	4	27	5
Invasive lobular carcinoma (n=7)	-	3	4	1	1	5	-	7	1	6	-	-	6	1
Inflammatary carcinoma (n=3)	-	-	3	-	-	3	-	3	-	-	3	-	3	-
Invasive tubular carcinoma (n=3)	-	-	3	-	1	2	-	3	-	-	3	-	3	-
Mucinous carcinoma (n=2)	-	1	1	-	-	2	2	-	2	-	-	-	-	2

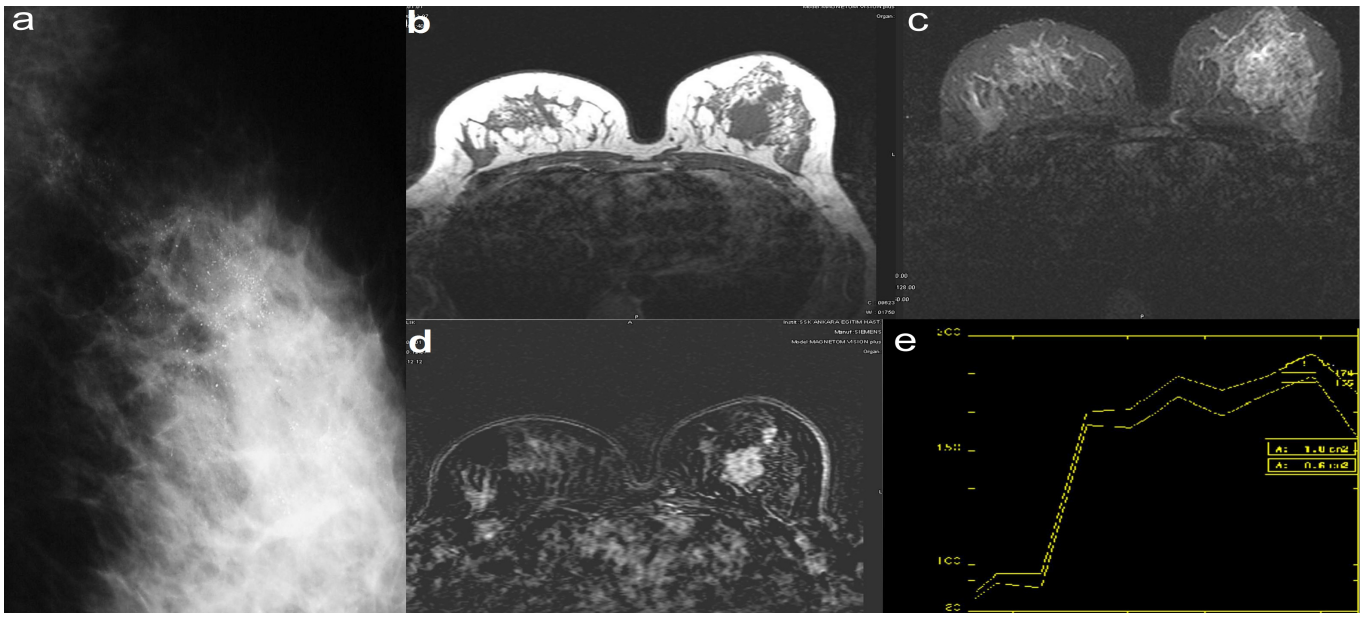

Figure 1. On left mediolateral oblique mammography (a) of a 47-year-old female with invasive ductal carcinoma, lesion with irregular contours and pleomorphic calcifications is seen in the superior outer quadrant of the left breast. On MRI, the mass is hypointense on T1-weighted image (b) and hyperintense on T2-weighted TIRM image (c), showing prominent signal enhancement on dynamic contrast-enhanced T1-weighted subtracted image (d). The time signal intensity curve of the lesion shows a type 2 time course (plateau), with a moderate, early period contrast enhancement rate between 60–80%, (e).

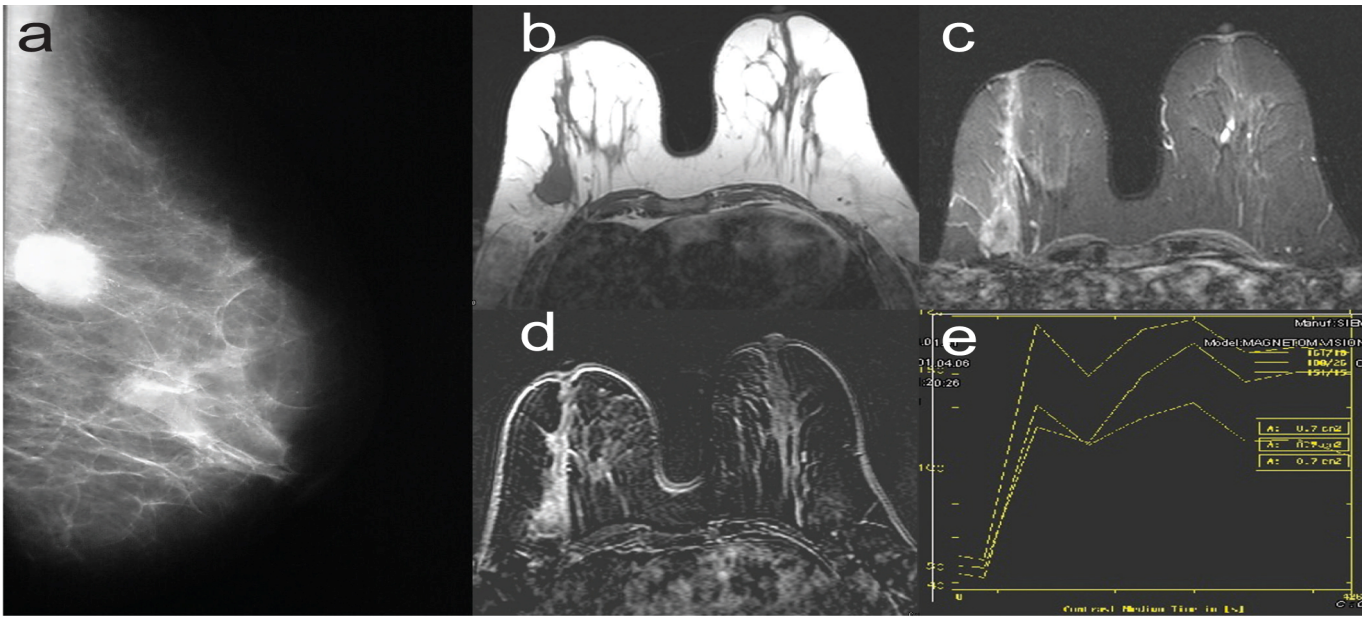

Figure 2. On right mediolateral oblique mammography (a) of a 55-year-old female with invasive ductal carcinoma, a spiculated and irregularly contoured, dense mass is seen in the superior outer quadrant of the right breast. On MRI, the mass is hypointense on T1-weighted image (b) and hyperintense on T2-weighted TIRM image (c), showing prominent signal enhancement on dynamic contrast-enhanced T1-weighted subtracted image (d). The time-signal intensity curve of the lesion shows a type 3 time course (wash-out), with an early period contrast enhancement rate above 80% (e).

The contrast enhancement features and morphological characteristics of the lesions: On DCE MRI, inner contrast enhancement of five (9.8%) lesions were homogeneous whilst inner contrast enhancement of 46 (90.2%) lesions were heterogeneous. Of the homogeneously contrast-enhanced lesions, three were invasive ductal carcinoma, and two were mucinous carcinoma. The intensity of inner contrast enhancement of four (7.7%) lesions were weak, while 29 (55.8%) were medium. Strong contrast enhancement was observed in 19 (36.5%) lesions. Morphologically, borders of 18 (35.3%) lesions were spiculated and of 26 (51%) were irregular. Besides, borders of five (9.8%) lesions were lobular and of two (3.9%) were smooth. Of 51 lesions, 47 were hypointense on T1-weighted images. Contours and signal properties of four (4/51) lesions could not help differentiate them from breast parenchyma.

Early-phase contrast enhancement rates: On DCE MRI, early-phase (first minute) contrast enhancement rates were as follows: Above 80% for 39 (76.5%) lesions, more than 60% and less than or equal to 80% for nine (17.6%) lesions and less than or equal to 60% for three (5.9%) lesions. Of the lesions with contrast enhancement less than or equal to 60%, two were invasive ductal carcinoma, and one was invasive lobular carcinoma.

Late postcontrast phase time-signal intensity curve patterns: Time-signal intensity curve of one (2%) lesion, which was invasive ductal carcinoma showed a type 1 time course (steady). Time-signal intensity curves of 15 (29.4%) lesions showed type 2 time course (plateau) and of 35 (68.6%) lesions showed type 3 time course (wash-out). Contrast enhancement was from central towards peripheral (centrifugal) in eight (15.7%) lesions, whereas it was from peripheral towards central (centripetal) in 39 (76.5%) lesions. Of the eight lesions with contrast enhancement from central towards peripheral, five were invasive ductal carcinoma, one was invasive lobular carcinoma, and two were mucinous carcinoma. In four (7.8%) lesions, diffuse and heterogeneous contrast enhancement was observed.

Discussion

Mammography is a conventional method widely used both for diagnosis and detection of breast cancer in symptomatic patients and for screening purposes. Pathological microcalcifications on mammography are among the most important diagnostic clues for the detection of malignant breast lesions. However, the sensitivity of mammography in characterization of lesions in dense breasts is relatively low. Similarity in the features of benign and malignant lesions on mammography is another disadvantage. Although mammography and US are complementary modalities in the imaging of breast lesions, US cannot determine microcalcifications, and is rather a user-dependent method (3, 4). Recently, the use of contrast-enhanced MRI of breast lesions has been shown to provide unique and significant data in patients who were initially evaluated by mammography and US. This is because that MRI can produce 3D, multiplanary (axial, coronal and sagittal) and DCE images, which can be used to evaluate both breasts, both axillas and the thorax wall. Its being free of ionizing radiation is another superiority as compared to mammography. Studies showed that sensitivity of MRI is high, whereas its specificity is relatively low. Specificity of MRI was reported to be between 37%–97% (6–8). The sensitivity and specificity of MRI in detection of ductal carcinoma in situ (DCIS) is lower than its sensitivity and specificity for invasive carcinomas (9). Rate of variability of the results may depend on the magnetic field power, imaging parameters, patient selection, image interpretation and histological variability of the benign and malignant lesions (10). Studies showed that T1-weighted DCE, magnetic resonance spectroscopy (MRS) and T2*-weighted sequence could be used in combination, in order to improve specificity and sensitivity of MRI. Huang et al. (9) obtained successful results in terms of specificity and sensitivity in the evaluation of breast cancers by using DCE MRI, MRS and T2-weighted perfusion in combination.

The morphological characteristics of the lesions can be used to distinguish between benign and malignant breast lesions in selective cases. It was reported that the specificity of morphological images varies between 70–80%. Irregular contours and spiculated mass are meaningful in terms of malignancy, and have high positive predictive values (11–14). Regular and lobular contours are meaningful in terms of benignity, and negative predictivity value for malignancy is close to 90% (11–13). On DCE MRI, peripheral rim or rim-like contrast enhancement feature is meaningful in terms of malignancy. In the present study, peripheral rim contrast enhancement, spiculated and irregular contours, heterogeneous inner contrast enhancement, and enhancement from peripheral to central were all meaningful in terms of malignancy and were in

consistence with literature. When compared with conventional MRI, DCE MRI increases the specificity in distinguishing the lesions (8, 15). Both quantitative and qualitative assessments can be made by using this method. Following injection of contrast agent, an immediate increase in time-signal intensity curve followed by wash-out occurs in malignant lesions, while a slower steady increase without wash-out in enhancement occurs in benign lesions (16). In the present study, the increase in the signal intensity ratio in early stage (first minute after administrating the contrast agent) was consistent with the literature in terms of malignancy. Kuhl et al. (15) reported significant contrast enhancement in 92/101 malignant lesions (over 80%). On DCE MRI, false negative and false positive results may occur. To illustrate, 10–15% of invasive carcinomas may show slow and diffusive contrast enhancement (17). Furthermore, merely significant contrast enhancement may occur in benign cases. A slow and late contrast enhancement in the lesion cannot eliminate the malignancy at 100% safety. Therefore, such conditions should be taken into account during the interpretation of the lesions. According to interim and late stage visual assessment of time-signal intensity curve in the study conducted by Kuhl et al. (15), 57/101 (57.4%) malignant lesions showed type 3 time course, besides 34/101 (33.6%) lesions showed type 2 time course. Type 1 time course was present in 9/101 (8.9 %) lesions. In the study conducted by Kinkel et al. (18), 29/34 (89%) malignant lesions and three benign lesions (atypical epithelial hyperplasia, intraductal papilloma, benign granular cell tumor) showed type 3 curve pattern. Boetes et al. (19) achieved high sensitivity, specificity and diagnostic accuracy (95%, 86%, 93%) in distinguishing benign and malignant lesions with Turbo FLASH sequence. In the study conducted by Ikeda et al. (20), false positive and false negative results were found to be related with benign and malignant breast lesions. Some lesions such as DCIS, mucinous carcinoma, lobular carcinoma, lobular adenosis and ductal adenosis, fibroadenoma and intraductal papilloma, can be confused in terms diagnosis. Also, scirrhous carcinoma may be confused with benign lesions because it contains intensive fibrotic tissue. Studies show that benign lesions rich in vascular structures or malignant lesions rich in fibrotic tissue cause difficulties in making accurate diagnosis. In the present study, one of our malignant lesions showed type 1 time course. More accurate results can be obtained if lesion morphology and contrast enhancement kinetics in DCE T1-weighted sequences, are evaluated together.

Recently, breast MRI studies including other emerging techniques such as MRS, diffusion MRI, perfusion MRI and magnetic resonance elastography have been conducted. These relatively newer techniques and DCE MRI, together may increase sensitivity, specificity and diagnostic accuracy in differential diagnosis of breast lesions. However, there is need for further studies involving greater number of patients for routine use of these modalities. Also the use of new modalities requires additional cost and time. In the present study, the absence of mentioned MRI modalities which could be used in combination with DCE MRI, is considered as a limitation. The absence of benign lesions in the present study and being unable to compare the DCE MRI findings of both benign and malignant lesions are other limitations of our study.

In conclusion, 3D DCE MRI used together with conventional imaging methods (mammography, US), provide assessment of morphological characteristics and contrast enhancement kinetics of malignant breast lesions, and is a useful method in their diagnosis.

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