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FULL PAPER

Stromal fibrosis: imaging features with diagnostic contribution of diffusion-weighted MRI

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Objective: To describe magnetic resonance imaging (MRI) and ultrasonography findings of breast stromal fibrosis (SF) and compare apparent diffusion coefficient (ADC) stromal fibrosis values with breast cancer and normal parenchyma.

Methods: 45 patients (ages 22–74) with histopathologically proven SF who underwent MRI were included in this study. Their MRI and ultrasonography features were examined and categorized. The mean ADC values for SF, contralateral normal parenchyma, and breast malignancy of the control group values were calculated and compared among each other.

Results: The vast majority of SF on sonography showed features suggestive of malignancy: (1) irregular in shape 25/45 (55%); (2) indistinct in margin 27/45 (60%); and (3) hypoechoic 39/45 (87%) with posterior acoustic shadowing 11/45 (24%). An SF MRI showed a mass in 12/45 (26%) and non-mass enhancement in 33/45 (74%), mostly with irregular (8/12; 67%) shape. Non-mass lesions showed heterogeneous (12/33), clumped (9/33), and homogenous (9/33) enhancement. The initial SF contrast uptake rate varied between slow (57%), rapid

(22%), and medium (21%). Delayed SF enhancement may be persistent (66%) or plateau (34%). Small cysts were located around/near 21 (47%) of lesions. Ductal ectasia was found in 14 (31%) of all patients. Mean ADCs of parenchyma, SF, and malignancy were 1.32 ± 0.32 , 1.23 ± 0.25 , and $0.99 \pm 0.24 \times 10^{-3} \text{ mm}^2 \text{ sec}^{-1}$, respectively.

Conclusion: SF often mimics breast carcinoma on imaging and leads the radiology–pathology disagreement. In terms of distinguishing SF from malignancy, ADC could be a significant and promising value in diffusion-weighted MRI along with conventional sequences. Slow initial uptake with delayed persistent contrast enhancement in a non-mass lesion with relatively higher ADC values are very helpful for differentiating SF from malignancy. The presence of small cysts and ductal ectasia were common findings around/near the SF.

Advances in knowledge: A quantitative analysis for measuring ADC values along with additional MRI features can be very helpful in distinguishing SF from malignant lesions.

INTRODUCTION

Stromal fibrosis of the breast is a benign histopathological diagnosis characterized by obliteration of mammary ducts and lobules and proliferation of fibrous stroma with atrophy.¹ This diagnosis is a rare finding obtained from a percutaneous breast biopsy with an incidence ranging from 2.1 to 9.0% depending on the series.^{2,3} Stromal fibrosis (SF) pathogenesis is unknown. However, hormonal stimulation of fibroelastic tissue is considered as the most likely cause, and most reported patients were premenopausal.⁴ SF may present as a palpable mass or a clinically occult and image-detected abnormality.^{4,5}

SF has a wide spectrum of imaging appearances on mammography (MG) and ultrasonography.^{5,6} SF also has

a variety of magnetic resonance imaging (MRI) spectral features that often mimic breast carcinoma, and a limited number of reports have evaluated SF MRI features in the literature.^{6–10} There is no generally accepted consensus on SF management. Histopathological SF diagnosis is acceptable in the absence of imaging features that are suspicious for malignancy. Cancer-related imaging features in histopathologically proven SF cases will raise doubt as to the correct diagnosis.

Diffusion-weighted imaging (DWI) has been a promising imaging modality in differentiating malignant from benign breast lesions by measuring the apparent diffusion coefficient (ADC).^{11,12} Diffusion-weighted SF image findings have not yet been clearly described, and very little is

known about SF DWI features. ADC values can help diagnose SF by assisting in benign–malignant discrimination that is not possible with conventional MRI findings and may bring clarity in suspected SF cases.

In this study, we aimed to evaluate SF MRI features, analyze the mean SF ADC values, and compare those with the contralateral normal breast parenchyma or malignancy to determine if additional information is provided by DWI. An additional objective was to describe the spectrum of imaging findings regarding SF on ultrasonography and MRI.

METHODS AND MATERIALS

Study design and patient populations

A total of 45 patients with a histopathological primary SF diagnosis, who underwent breast MRI were recruited for this study from January 2015 to July 2016. This study was performed prospectively, and patients were enrolled consecutively within this period. SF was the only primary diagnosis in patients' pathological reports. Insignificant amounts of other benign histopathological entities such as ductal ectasia ($n = 10$) with or without ductal hyperplasia, adenosis ($n = 6$), and apocrine metaplasia ($n = 4$) were found together with SF after detailed pathological evaluations at our pathology clinic. Cases of SF with concurrent malignancy or those that had upgraded to cancer were excluded. 33 patients were admitted to the radiology department with symptoms of a palpable mass or any other clinical presentations. SF was detected during 12 patients' screening evaluations.

MG was not included in the study because we could not get all of mammograms, since they had been examined in different centers. Only 34 patients had mammographies through our system. 23 of 34 patients were >40 years. MG was performed as screening in 12 patients and diagnostic in 11 patients. 11 patients <40 years underwent MG as part of a diagnostic evaluation.

The control group consisted of age-matched patients who had been diagnosed with early stage (T_1 or T_2 classification) invasive carcinoma within the period consecutively presumed to reflect the general population. Most of the masses in the control group were histopathologically proven as invasive ductal carcinoma (80%), and the remaining ones were either invasive lobular carcinoma (10%) or mixed type (10%), including ductal and lobular components.

Prior approval and written informed consents were obtained from patients, and the study was approved by the institutional ethics committee.

Imaging

Ultrasonography

Ultrasonography examinations (Acuson Antares, Siemens, Germany) were performed on all patients using a high-resolution linear probe with 12 MHz frequency within the same month before their MRIs. We evaluated the size, shape, margin, echogenicity, acoustic enhancement, and/or shadowing of the lesions using ultrasonography in addition to patients' ages and menstrual statuses and accompanying histopathological entities.

All biopsies were performed under ultrasonography using a 14 G core needle biopsy (minimum of four cores per lesion). No clip was added to the lesions after biopsy.

Magnetic resonance imaging

MRI investigations were performed using a 1.5 T whole body MRI scanner (Achieva, Philips Medical Systems, Best, Netherlands). A patient was placed in the prone position, and a dedicated four-channel phased-array bilateral breast coil was used. Each MRI examination included fat saturated T_2 weighted images in the axial plane obtained using turbo spin echo sequences [repetition time/echo time (TR/TE): 4135/120 ms; matrix, 272×224 ; field of view (FOV), 340×340 mm; number of excitations (NEX), 2; slice thickness, 3 mm], T_1 weighted images (TR/TE: 497/10 ms), and matrix (272×267 ; FOV, 340×400 mm; NEX, 2; slice thickness, 3 mm) in the axial planes. In the T_1 weighted turbo field echo three-dimensional sequences (TR/TE, 6.9/3.4 ms; matrix, 340×338 ; NEX, 2; FOV, 340×340 mm), dynamic axial images were taken once before and six times after the administration of the gadolinium-based contrast agent, which was infused as 0.1 mmol kg^{-1} dosage. Subtraction series were obtained, and the time–signal intensity curves of the lesions were drawn and interpreted. A sagittal post-contrast turbo field echo three-dimensional sequence (TR/TE, 7.3/3.6 ms; matrix, 248×250 ; NEX, 2; FOV, 200×200 mm) was taken after contrast. DWIs were acquired in the transverse plane using a single-shot echo planar imaging sequence with the diffusion gradients in the x , y , and z planes at b values of 0, 400, and 800 respectively (TR/TE, 15,189/86 ms; matrix, 228×226 ; FOV, 340×340 mm; NEX, 2; slice thickness, 3 mm). ADC maps were automatically created.

Image interpretation

Two experienced breast radiologists with 6 and 10 years experience in breast imaging, who were blinded to patients' results, evaluated all MR images at the same time. One radiologist with 6 years experience performed all ultrasonography examinations. The findings were characterized by consensus according to the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) Atlas 5th edition.¹³ The signal intensity on T_1 - and T_2 W images, the quadrant, and SF distribution, including SF long and short diameters, shape, margin, internal enhancement, initial contrast uptake, late contrast enhancement, presence of cyst formation around/near the SF, and accompanying ductal dilatations were documented in addition to either a mass or non-mass form. Ducts > 2 mm were assessed in the dilated state. We defined as around/near the SF in cases in which cysts were present within the 4 cm area around the lesion.

The mean ADC values were calculated from the ADC map by drawing the entire contour of the lesion and region of interest from the parenchyma of the contralateral breast. We also calculated the mean ADC values of 45 patients diagnosed with invasive carcinoma within the control group. The region of interest was manually placed within the solid portion of the malignant lesions. ADC measurements were performed by radiologists blinded to patients' histopathological results. The mean ADC values for SF, normal breast parenchyma of the same patient, and invasive cancer in the control group were measured three times. The average ADC values were calculated.

Figure 1. Stromal fibrosis in a 37-year-old female. (a) Ultrasonography shows (arrow) irregular shaped hypoechoic mass with indistinct margins. (b, c) Lesion is hypointense on T_2 weighted image (arrow) and presents heterogeneous enhancement as non-mass stromal fibrosis on contrast-enhanced fat suppressed sagittal T_1 W MR image (arrow). (d, e) The lesion (arrow) is hyperintense on axial diffusion-weighted image and has a low ADC on an ADC map. ADC, apparent diffusion coefficient.

Statistical analysis

All statistical analyses were performed using statistical software SPSS software v. 21 (SPSS Inc, Chicago, IL). Data are presented as mean $\pm$ standard deviation. The frequencies of the involved quadrant, presence of cyst and ductal dilatation, and MRI findings were also analyzed. The Kolmogorov–Smirnov test was used to evaluate the mean ADC value distribution. The independent sample *t*-test was applied to compare the mean SF ADC values with the contralateral normal breast parenchyma and breast cancer. ADC values of normal breast parenchyma were also compared to breast cancer. Receiver operator characteristic (ROC) curves were calculated regarding differentiation of malignancy from SF based on ADC values. *p* values <0.05 were accepted as statistically significant.

RESULTS

Patient population

SF detected with ultrasonography was histopathologically proven using ultrasonography-guided biopsies in 43 lesions and by excisional biopsies in 2 lesions. MRIs were performed for all patients, and three of them were performed before the biopsy. The interval between biopsy and MRI ranged from 2 to 4 weeks in order not to cause a change in ADC values. SF patients were between 22 and 74 years (mean: 44.4 ± 9.35 years). 27 (69%) of the 39 patients were ≤ 55 years, and 30 (66%) of 45 patients were premenopausal. There were no significant differences between mean ages of the SF and malignancy groups (44.4 ± 1.39 years and 45.6 ± 1.21 , respectively; $p > 0.05$).

60% of the SF cases were located in the right breast and the remaining were left-side located. The majority of the lesions in both breasts ($n = 18$) were in the upper and outer quadrant, and three SFs were located in the retroareolar region. The mean diameters calculated on MRI for short and long axes were 13.6 ± 7.95 and 23.46 ± 15.01 mm, respectively.

20 of 34 patients had dense parenchyma without any other detectable findings on MG. The mammographic features of the 11 lesions had variable appearance: (1) 6/11 (55%) were oval-round in shape and (2) 5/11 (45%) had circumscribed or partly circumscribed margins. Three lesions had more suspicious features consisting of irregular shape and indistinct margins with amorphous/punctate calcifications. Two of them were evaluated as focal asymmetry on MGs.

Imaging

Ultrasonography

The morphological ultrasonography characteristics of SF included irregular shapes in 25/45 cases (55%), oval in 15/45 (33%), and round in 5/45 (11%). The margins were indistinct in 27/45 (60%), microlobulated in 9/45 (20%), and circumscribed in 9/45 (20%). No lesions with spiculated contours were found. The majority of lesions 39/45 (87%) were hypoechoic to the parenchyma, which suggested a fibrotic process, and most of the remaining lesions 4/45 (9%) were isoechoic. Only two patients had hyperechoic lesions with heterogeneous internal structure. 80% of the lesions (36/45) had a heterogeneous internal structure

Table 1. MRI characteristics of SF calculated by frequency and percent

Descriptor	Category	Frequency (n)	Percent (%)
Pattern of breast parenchyma	Fatty	4	8
	Scattered fibroglandular	8	18
	Heterogeneous fibroglandular	15	33
	Extreme fibroglandular	18	40
Background enhancement	Mild	13	28
	Moderate	13	28
	Marked	19	42
Distribution of SF (non-mass; 33)	Focal	9	20
	Regional	9	20
	Segmental	15	60
Accompanying ductal ectasia	Absent	31	69
	Present	14	31
Cyst number near the SF	None	24	53
	1–5	12	27
	6–10	5	10
	11–15	2	5
	16–27	2	5
Shape (mass; 12)	Round	1	8
	Oval	3	25
	Irregular	8	67
Border	Smooth	10	22
	Irregular	35	78
	Spiculated	0	0
Signal on T_2W image	Hyperintense	10	23
	Isointense	26	57
	Hypointense	9	20
Mass formation	Mass	12	26
	Non-mass	33	74
Initial contrast uptake	Rapid	10	22
	Medium	9	21
	Slow	26	57
Delayed contrast enhancement	Persistent	30	66
	Plateau	15	34

SF, stromal fibrosis.

because of the distribution of the fibrotic area within the breast parenchyma. In addition to hypoechogenicity, acoustic shadowing was found in 11 (24%) of all of the patients.

Magnetic resonance imaging

The amount of fibroglandular tissue in patients with SF was evaluated on MRI. Breast composition was almost entirely fat in 4/45

(8%), scattered fibroglandular tissue in 8/45 (18%), heterogeneous fibroglandular tissue in 15/45 (33%), and extreme fibroglandular tissue in 18/45 (40%) of patients. Background enhancement was marked in 19/45 (42%) of patients and either mild or moderate in the remaining patients as seen on an optimal MRI. SF presented as a mass in 12/45 (26%) and non-mass enhancement in 33/45 (74%) patients (Figure 1). The shapes of the masses were irregular in 8/12 (67%), oval in 3/12 (25%), and round in 1/12 (8%). The distribution of non-mass enhancing SF was segmental in 15/33 (60%), focal in 9/33 (20%), and regional in 9/33 (20%) of all of the SF patients. No lesions with linear or diffuse distributions were found. The internal enhancement patterns of non-mass SF were homogenous in 9/33 (20%), heterogeneous in 12/33 (48%), clustered ring in 3/33 (12%), and clumped in 9/33 (20%). All of the lesions showed low-to-medium signal intensity on T_1W images. Most lesions 26/45 (57%) were isointense, and the remaining were either hyperintense 10/45 (23%) or hypointense 9/45 (20%) to the parenchyma on T_2W images. Dynamic contrast-enhanced images showed that the rate of initial contrast uptake varied between rapid 10/45 (22%), medium 9/45 (21%), and slow 26/45 (57%). Delayed contrast enhancement of either mass or non-mass enhancing SF may be persistent 30/45 (66%) or plateau 15/45 (34%). No lesions showed a washout pattern. Ductal ectasia was found in 14/45 (31%) of all patients. Millimetric cyst formations were located around/near 21/45 (47%) of the lesions. The number of cysts varied between 1 and 5 in 12/45 (27%) patients, 6 and 10 in 5/45 (10%), 11 and 15 in 2/45 (5%), and 16 and 27 in 2/45 (5%) patients (Table 1). SF patients had a follow-up visit every 6 months for at least 2 years with only ultrasonography in 15, MRI in 27, and with both in 3 patients. Patients triaged between ultrasonography and MRI follow-ups relevant to patient's risk factors and lesion features. Follow-up examinations were negative for malignancy.

Statistical analyses

ADCs measured for normal parenchyma, SF, and malignancy were normally distributed based on evaluations of skewness, kurtosis, and equality of the variances. The mean ADCs of normal parenchyma, SF, and malignancy were 1.32 ± 0.32 , 1.23 ± 0.25 , and $0.99 \pm 0.24 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, respectively (Table 2) (Figure 2). There were no significant differences between the mean ADC values of SF and normal parenchyma ($p > 0.05$). (Figure 3). However, the differences between the mean ADC values for SF and malignancy were highly significant ($p < 0.001$) (Table 2). The optimal cut-off value for differentiating malignancy from SF was found to be $1.1 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ with a calculated sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 80, 70, 73, 71, and 68%, respectively. When receiver operator characteristic curves regarding ADC were plotted, the area under the curve for differentiating SF from malignancy was found to be 0.801 [95% confidence interval (0.71–0.88), $p : 0.001$] (Figure 4). Also, the differences between the mean ADC values for normal parenchyma and malignancy were highly significant ($p < 0.001$) (Table 1).

DISCUSSION

Breast SF is a benign histopathological diagnosis characterized by a localized area of fibrous tissue associated

Table 2. Descriptive statistics based on ADC values and comparison of mean ADC values among SF to the parenchyma and malignancy

Descriptive statistics						Independent samples <i>t</i> test			
		N	Min	Max	Mean	Std. dev.	Sig. (<i>p</i>)	<i>t</i>	Samples
ADC	Parenchyma	45	0.78	2.13	1.32	0.32	0.13	-1.5	Parenchyma <i>vs</i> stromal fibrosis
	Stromal fibrosis	45	0.8	1.94	1.23	0.25	0.001	4.4	Malignancy <i>vs</i> stromal fibrosis
	Malignancy	45	0.6	1.75	0.99	0.24	0.001	6	Malignancy <i>vs</i> parenchyma

ADC, apparent diffusion coefficient; SF, stromal fibrosis.

Number of age matched participants and minimum (min), maximum (max), mean and standard deviation (std. dev.) of ADC values for stromal fibrosis, parenchyma and malignancy were given. Mean ADC values were significantly higher in stromal fibrosis when compared to malignancy. There was no significant difference between stromal fibrosis and breast parenchyma in terms of apparent diffusion coefficient.

with hypoplastic-obiterated mammary ducts and lobules.² However, more recent reports have described mostly non-palpable clinical presentation, ranging from 65 to 96% of cases in some series with common use of MG, ultrasonography, and MRI.^{2,5,6}

Biopsy would be sufficient for a benign diagnosis in many cases, if the results were in agreement and follow ups would not be necessary for these lesions. However, SF diagnosed via percutaneous core biopsy can be related to the undersampling

of an adjacent breast cancer.¹⁴ Malik et al showed an upgrade rate of 7% in biopsy-proven stromal fibrosis and a false negative rate in 2% of SF cases with features in agreement with a benign diagnosis, which were subsequently upgraded to malignancy.¹⁴ With the diversity of the imaging findings and this pathology-based suspicion, absence of consensus guidelines for management of the SF histopathological diagnosis has confounded any of our ideas about how to manage SF. Repeat biopsy or surgical excision is recommended in the cases of radiology-pathology discordance.

Figure 2. Box and whisker plots represent median ADC values of normal breast parenchyma, SF, and malignancy groups. Median ADC values in malignancy group were found to be lower both in the parenchyma and also SF. There were no statistically significance among the mean ADC values of parenchyma and the SF group. ADC, apparent diffusion coefficient; SF, stromal fibrosis.

Figure 3. A 47-year-old female had stromal fibrosis in the left breast. (a) Ultrasonography shows (arrow) irregular shaped heterogeneous hypoechoic lesion (arrows) with presence of nearby small cysts (stars). (b) T_2 weighted image with fat suppression shows hypointense lesion (arrow) in the inner-inferior quadrant of the breast. (c, d) Subtraction images (2. and 7. s) show heterogeneous enhancement with segmental distribution of non-mass lesion. Time-signal intensity curve shows slow initial enhancement with persistent pattern (gradual and progressive enhancement). (e) ADC map depicts similar mean ADC value of SF ($1.24 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) (white arrow) compared with the contralateral normal parenchyma ($1.18 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) (black arrow). ADC, apparent diffusion coefficient.

SF MG and ultrasonography features are nonspecific and variable as described in the literature.^{2,6} The margins of the present mass lesions of SF have been described as non-circumscribed (80%), and internal structure has been described as hypoechogenic (87%) with heterogeneity (80%) as seen on ultrasonography. As described in the literature and similar to our findings, a minority of patients may present with well-circumscribed benign-appearing masses.^{15,16} In contrast to these studies' findings, Taskin et al reported that 63% of focal fibrosis cases were categorized as BI-RADS III according to MG and ultrasonography findings, and

Sklair-Levy et al reported that the margins were circumscribed in 35 (56%) and ill-defined or microlobulated in 28 (44%) lesions in their series.^{2,6}

Our results suggest that most lesions presented as non-mass enhancement (33/45; 74%) on MRI. These lesions were distributed as segmental in 15/33 (60%), focal in 9/33 (20%), and regional in 9/33 (20%) patients. SF in the form of non-mass enhancement with segmental distribution is very suspicious for mastitis and malignancy, especially for ductal carcinoma

Figure 4. ROC curve revealing diagnostic performance of ADC in differentiating SF from malignancy is given. The area under the curve was 0.801 [95% confidence interval (0.71–0.88), p : 0.001]. ROC, receiver operator characteristic.

in situ on MRI. For this reason, a clinical history should be sought for mastitis and segmental pleomorphic and fine linear microcalcifications on MG should be investigated to differentiate between malignancy and SF. Although MG is not included in our research, we observed clustered amorphous/punctate in 3 of 34 patients, but they had low suspect morphology and distribution in terms of malignancy. Background parenchymal enhancement (BPE) is a dynamic process, varying among females but also within the same female over time.¹⁷ When BPE is focal or asymmetric, it may be confused with non-mass enhancement such as SF. It is unusual for BPE to exhibit delayed plateau or washout kinetic curves; however, it was reported that the more suspicious kinetic curves can be present in benign mastopathic conditions.^{18,19} Lee et al reported that the most prevalent SF features, when seen as a mass on MRI, were round or oval shape with irregular or spiculated margins, rapid or medium rate of initial contrast uptake, and plateau or washout curves.⁷ 8 of their 12 non-mass enhancements showed these suspicious features, including clumped, linear or ductal enhancement, and segmental enhancement.⁷ Lee et al and our prospective study revealed the way in which these suspicious features could be misleading with respect to the MRI interpretation in a group of SF patients.⁷ However, the presence of cysts in and ductal ectasia near/around the SF in our study may help to differentiate SF from malignancy (Figure 5). Morris and Liberman illustrated six cases of SF on MRI that were small foci or masses.⁸ In a study concerning the utility of breast MRI

Figure 5. A 41-year-old female with stromal fibrosis in the right breast. (a) Ultrasonography shows (arrows) indistinct, heterogeneous, hypoechoic mass (white arrows) adjacent to normal parenchyma (black arrow) and presence of nearby small cysts (stars). (b) Subtraction image of second of the six image shows clumped enhancement with segmental distribution. (c) 1 year and 6 months later, the lesion was observed as stable in size on MRI controls.

in patients with occult primary breast cancer, Buchanan et al reported three SF cases that appeared as enhancing nodules and masses.¹⁶ Previous studies have shown that the kinetic SF features may vary in a manner similar to cancer and benign masses and can help a little with the interpretation of the findings.⁷ Unlike findings from this report, our study showed kinetic SF features with mostly benign features such as slow initial contrast uptake and persistent delayed enhancement. In cases in which there is radiological and/or pathological disagreement after biopsy, kinetic features can help swing the decision of SF.

The use of DWI, which reflects the thermal diffusion of water molecules (Brownian motion), improves conventional MRI performance for differentiating malignant from benign breast lesions. Compatible with previous studies, this study revealed that the ADC values of benign lesions were significantly higher than that of malignant lesions.^{11,20–22} The present study completes the missing portion of existing data regarding SF by showing that ADC values may help to differentiate benign from malignant lesions. Our results suggest that the mean SF ADC value ($1.23 \pm 0.25 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) was significantly higher than that in breast cancer cases ($0.99 \pm 0.24 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$). However, the mean SF ADC value was closest to the breast parenchyma ADC value ($1.32 \pm 0.32 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$). Therefore, there are no significant differences when ADC values are displayed for SF and breast parenchyma. These results show that a quantitative analysis of ADC values can be used to distinguish SF from malignancy.

Several studies have reported substantial variability in the mean ADC values for breast lesions corresponding to benign and malignant lesions, and consequently no consistent threshold ADC values have been reported to differentiate malignant from benign lesions.^{23–25} Various factors can influence the ADC values: (1) specific pulse sequence; (2) *b*-values; (3) magnetic field strength; (4) application of diffusion gradients before or after contrast administration; (5) the nature of the lesion; and (6) breast physiological variation.²⁴ Bogner et al reported that using *b*-values did not provide an advantage, and they reported the ideal *b*-value as 850 s mm^{-2} .²⁶ We used two different *b* values ($b = 400, 800 \text{ s mm}^{-2}$) to suppress

normal tissue as much as possible and to easily demonstrate hypercellular lesions.

A study limitation was the lack of accounting for patients' menstrual cycles, and no information about administration of exogenous hormones such as hormone replacement therapy was taken into consideration during the MRI and biopsy procedure planning. However, although ADC values of normal fibroglandular breast tissue demonstrate changes during menstruation, these changes were not statistically significant.²⁷ The SF ADC value is higher than breast cancer, but after considering the standard deviation, the range of ADC for SF is 0.98–1.48, while the range of ADC for breast cancer is 0.75–1.23. Therefore, breast cancer may have an ADC value between 0.98 and 1.23 and fall into the range of the SF ADC values. Considerable overlap of these values seems to exist. This may cause difficulty in using ADC values to differentiate benign from malignant lesions in daily practice. This is an important limitation for this study. Further studies are required to establish a standard ADC value for use as a threshold in clinical settings and to validate our findings in a larger series.

In conclusion, SF may mimic malignancy on imaging and leads the radiology–pathology disagreement. ADC values can be used to differentiate SF from malignant lesions. Slow initial uptake with delayed persistent contrast enhancement in a non-mass lesion and the presence of small cysts and ductal ectasia may help to distinguish SF from malignancy. The combined protocol of conventional MRI and DWI has the potential to increase correct diagnosis rates.

ETHICAL APPROVAL

This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONSENT

Informed consent was obtained from all individual participants included in the study.

REFERENCES

- Rosen PP. Benign mesenchymal neoplasms. In: *Rosen's breast pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009. pp. 838–9.
- Sklair-Levy M, Samuels TH, Catzavelos C, Hamilton P, Shumak R. Stromal fibrosis of the breast. *AJR Am J Roentgenol* 2001; **177**: 573–7. doi: <https://doi.org/10.2214/ajr.177.3.1770573>
- You JK, Kim EK, Kwak JY, Kim MJ, Oh KK, Park BW, et al. Focal fibrosis of the breast diagnosed by a sonographically guided core biopsy of nonpalpable lesions: imaging findings and clinical relevance. *J Ultrasound Med* 2005; **24**: 1377–84.
- Harvey SC, Denison CM, Lester SC, DiPiro PJ, Smith DN, Meyer JE. Fibrous nodules found at large-core needle biopsy of the breast: imaging features. *Radiology* 1999; **211**: 535–40. doi: <https://doi.org/10.1148/radiology.211.2.r99ma42535>
- Revelon G, Sherman ME, Gatewood OM, Brem RF. Focal fibrosis of the breast: imaging characteristics and histopathologic correlation. *Radiology* 2000; **216**: 255–9. doi: <https://doi.org/10.1148/radiology.216.1.r00jl16255>
- Taskin F, Unsal A, Ozbas S, Erkus M, Karaman C. Fibrotic lesions of the breast: radiological findings and core-needle biopsy results. *Eur J Radiol* 2011; **80**: e231–e236. doi: <https://doi.org/10.1016/j.ejrad.2010.10.008>
- Lee SJ, Mahoney MC, Khan S. MRI features of stromal fibrosis of the breast with histopathologic correlation. *AJR Am J*

- Roentgenol* 2011; **197**: 755–62. doi: <https://doi.org/10.2214/AJR.11.6489>
8. Morris EA, Lieberman L. Benign lesions. In: *Breast MRI: diagnosis and intervention*. New York, NY: Springer-Verlag Science+Business Media; 2005. pp. 452–5.
 9. Gutierrez RL, DeMartini WB, Eby PR, Kurland BF, Peacock S, Lehman CD. BI-RADS lesion characteristics predict likelihood of malignancy in breast MRI for masses but not for nonmasslike enhancement. *AJR Am J Roentgenol* 2009; **193**: 994–1000. doi: <https://doi.org/10.2214/AJR.08.1983>
 10. Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. *J Magn Reson Imaging* 2002; **16**: 172–8. doi: <https://doi.org/10.1002/jmri.10140>
 11. Marini C, Iaconi C, Giannelli M, Cilotti A, Moretti M, Bartolozzi C. Quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesion. *Eur Radiol* 2007; **17**: 2646–55. doi: <https://doi.org/10.1007/s00330-007-0621-2>
 12. Guenin M. The low false-negative rate for stereotactic breast biopsy. *Radiology* 2000; **216**: 609–10. doi: <https://doi.org/10.1148/radiology.216.2.r00ma26609>
 13. Sickles EA, D'Orsi C. Follow-up and outcome monitoring. In: *ACR BIRADS® atlas, breast imaging and reporting and data system*. Reston, VA: American College of Radiology; 2013. pp. 27.
 14. Malik N, Lad S, Seely JM, Schweitzer ME. Underestimation of malignancy in biopsy-proven cases of stromal fibrosis. *Br J Radiol* 2014; **87**: 20140182. doi: <https://doi.org/10.1259/bjr.20140182>
 15. Lee CH, Philpotts LE, Horvath LJ, Tocino I. Follow-up of breast lesions diagnosed as benign with stereotactic core-needle biopsy: frequency of mammographic change and false-negative rate. *Radiology* 1999; **212**: 189–94. doi: <https://doi.org/10.1148/radiology.212.1.r99j42189>
 16. Buchanan CL, Morris EA, Dorn PL, Borgen PI, Van Zee KJ. Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. *Ann Surg Oncol* 2005; **12**: 1045–53. doi: <https://doi.org/10.1245/ASO.2005.03.520>
 17. Kuhl CK, Bieling HB, Gieseke J, Kreft BP, Sommer T, Lutterbey G, et al. Healthy premenopausal breast parenchyma in dynamic contrast-enhanced MR imaging of the breast: normal contrast medium enhancement and cyclical-phase dependency. *Radiology* 1997; **203**: 137–44. doi: <https://doi.org/10.1148/radiology.203.1.9122382>
 18. Giess CS, Yeh ED, Raza S, Birdwell RL. Background parenchymal enhancement at breast MR imaging: normal patterns, diagnostic challenges, and potential for false-positive and false-negative interpretation. *Radiographics* 2014; **34**: 234–47. doi: <https://doi.org/10.1148/rgr.341135034>
 19. Chen JH, Liu H, Baek HM, Nalcioğlu O, Su MY. Magnetic resonance imaging features of fibrocystic change of the breast. *Magn Reson Imaging* 2008; **26**: 1207–14. doi: <https://doi.org/10.1016/j.mri.2008.02.004>
 20. Woodhams R, Matsunaga K, Iwabuchi K, Kan S, Hata H, Kuranami M, et al. Diffusion-weighted imaging of malignant breast tumors: the usefulness of apparent diffusion coefficient (ADC) value and ADC map for the detection of malignant breast tumors and evaluation of cancer extension. *J Comput Assist Tomogr* 2005; **29**: 644–9.
 21. Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. *J Magn Reson Imaging* 2002; **16**: 172–8. doi: <https://doi.org/10.1002/jmri.10140>
 22. Hatakenaka M, Soeda H, Yabuuchi H, Matsuo Y, Kamitani T, Oda Y, et al. Apparent diffusion coefficients of breast tumors: clinical application. *Magn Reson Med Sci* 2008; **7**: 23–9. doi: <https://doi.org/10.2463/mrms.7.23>
 23. Rahbar H, Partridge SC, Demartini WB, Gutierrez RL, Allison KH, Peacock S, et al. In vivo assessment of ductal carcinoma in situ grade: a model incorporating dynamic contrast-enhanced and diffusion-weighted breast MR imaging parameters. *Radiology* 2012; **263**: 374–82. doi: <https://doi.org/10.1148/radiol.12111368>
 24. Thomassin-Naggara I, De Bazelaire C, Chopier J, Bazot M, Marsault C, Trop I. Diffusion-weighted MR imaging of the breast: advantages and pitfalls. *Eur J Radiol* 2013; **82**: 435–43. doi: <https://doi.org/10.1016/j.ejrad.2012.03.002>
 25. Hussein H, Chung C, Moshonov H, Miller N, Kulkarni SR, Scaranelo AM. Evaluation of apparent diffusion coefficient to predict grade, microinvasion, and invasion in ductal carcinoma in situ of the breast. *Acad Radiol* 2015; **22**: 1483–8. doi: <https://doi.org/10.1016/j.acra.2015.08.004>
 26. Bogner W, Gruber S, Pinker K, Grabner G, Stadlbauer A, Weber M, et al. Diffusion-weighted MR for differentiation of breast lesions at 3.0 T: how does selection of diffusion protocols affect diagnosis? *Radiology* 2009; **253**: 341–51. doi: <https://doi.org/10.1148/radiol.2532081718>
 27. Partridge SC, McKinnon GC, Henry RG, Hylton NM. Menstrual cycle variation of apparent diffusion coefficients measured in the normal breast using MRI. *J Magn Reson Imaging* 2001; **14**: 433–8. doi: <https://doi.org/10.1002/jmri.1204>