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Differentiation between Pure Mucinous Breast Carcinomas and Fibroadenomas with Strong High-Signal Intensity on T2-Weighted Images from Dynamic Contrast-Enhanced Magnetic Resonance Imaging

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Keywords

Pure mucinous breast carcinoma · Fibroadenoma · Dynamic contrast-enhanced magnetic resonance imaging · Breast cancers

Summary

Objective: This study aimed to identify characteristics that can differentiate between pure mucinous breast carcinomas (PMBCs) and fibroadenomas (FAs) with strong high-signal intensity on T2-weighted images (T2-SHi) from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). **Methods:** The DCE-MRI tumor characteristics were compared and analyzed between 35 PMBCs and 70 FAs with T2-SHi. **Results:** Multivariate analysis revealed that delayed enhancement pattern was the only significant independent predictor ($p = 0.007$). **Conclusion:** A delayed enhancement pattern is the most reliable characteristic for differentiating PMBCs from FAs with T2-SHi from DCE-MRI.

Introduction

Mucinous breast carcinoma (MBC) and fibroadenoma (FA) are two distinctive types of breast neoplasms. MBC is an uncommon variant of invasive ductal carcinoma and accounts for 1–7% of all breast cancers [1]. MBCs, which are characterized by much extracellular mucus secreted by the epithelial cells of the tumor, can be divided into pure and mixed forms on the basis of the proportion of mucin and tumor cells: Pure MBC (PMBC) is defined as a tumor with a mucinous component of more than 90%, whereas mixed MBC (MMBC) has a mucinous component of 50–90% mixed with infiltrating ductal epithelial components [2]. PMBCs comprise less than 2% of all breast cancers [3], and they tend to have less involvement of axillary lymph nodes and a better prognosis than MMBCs [4].

FAs, which contain both fibrous and epithelial components, are the most common benign neoplasm of the female breast [5]. About 40% of FAs have myxoid or edematous changes histopathologically [6]. On ultrasonography, myxoid or edematous FAs are often misdiagnosed as PMBCs. The misdiagnosis results from 2 factors: (1) The myxoid or edematous FAs may have expansive growth that produces a relatively high depth/width ratio predictive of a malignant tumor, and (2) both FAs and PMBCs have posterior echo enhancement caused by low attenuation and consequent high transmission of ultrasound through the myxoid or edematous component in FAs and the abundant mucus in PMBCs [6]. On mammography, PMBCs are often misdiagnosed as FAs because PMBCs have imaging characteristics resembling benignity, including a well-circumscribed margin and the absence of microcalcification [7]. Thus, differentiating PMBCs from myxoid or edematous FAs is difficult with conventional imaging.

With magnetic resonance imaging (MRI), FAs with abundant myxoid or edematous stroma rich in free water yield strong high-signal intensity on T2-weighted images (T2-SHi) similar to that of PMBCs [8]; thus, these two tumors may not be differentiated with T2-weighted images alone. Regardless of these diagnostic difficulties, accurate preoperative diagnosis is crucial because the lesions require very different therapeutic approaches: The majority of FAs can be left untreated or followed and only a minority need enucleation [5], whereas PMBCs require surgical excision, most often with breast-conserving therapy and sentinel lymph node biopsy [9].

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Imaging-guided core biopsy has been considered the first choice for most breast lesions that cannot be diagnosed with conventional imaging [10]. However, core biopsy specimens of FAs with extreme myxoid change of stroma can be misdiagnosed as MBCs histopathologically [11]. Moreover, breast biopsy is invasive, with risks of complications such as hematoma and infection [12].

Dynamic contrast-enhanced (DCE)-MRI is a mature technology that can be used to complement conventional imaging in the differential diagnosis of breast diseases [10]. DCE-MRI can provide tissue characterization and morphological features based on T1- and T2-weighted images; DCE-MRI can also provide information on tissue kinetic features, including the internal enhancement pattern, the initial enhancement increase, and the kinetic curve pattern. To our knowledge, only 1 report has described DCE-MRI to differentiate MBCs from FAs with T2-SHi [8], and that report included pure as well as mixed forms of MBCs. Thus, we conducted the present study to identify the DCE-MRI characteristics of PMBCs or FAs with T2-SHi that can help to differentiate between the two lesions.

Material and Methods

Patients

This retrospective review was approved by our institutional review board, and informed consent was waived. Between January 2014 and June 2016, 34 patients with 35 PMBCs diagnosed histopathologically after surgical resection and who had undergone breast MRI before operation were enrolled. Patients with PMBCs who received neoadjuvant chemotherapy were excluded. 69 patients with 70 FAs diagnosed by histopathology after surgical resection and who had homogeneous T2-SHi similar to that of PMBCs during the same period were also enrolled. T2-SHi was defined as the intensity that was the same as or higher than that of vessels in the breast [1]. The women who had PMBCs or FAs with T2-SHi were aged 49.7 ± 12.0 years (range, 23–74 years) and 43.2 ± 9.7 years (range, 17–62 years), respectively, which were statistically significantly different ($p = 0.004$).

MRI Examination

MRI of all patients was performed with the 1.5-Tesla system (Sigma Excite HD; GE Healthcare, USA) with a dedicated 8-channel high-definition breast coil. The patient lay in the prone position on the examination bed, with the bilateral breasts naturally hanging in 2 round holes of the breast coil during the examination. First, sagittal fat-saturated T2-weighted fast-spin echo images of the bilateral breasts were recorded, with the following parameters: repetition time/echo time, 4,040 ms/81 ms; echo train length, 19; slice thickness, 5 mm; slice gap, 1 mm; field of view, 220 mm; matrix size, 320 × 224; number of excitations, 2; imaging time, 1 min 41 s. Then, unenhanced and enhanced sequences of axial fat-saturated gradient recalled echo T1-weighted images were acquired with the following parameters: repetition time/echo time/inversion time, 6.1 ms/2.9 ms/13 ms; flip angle, 10°; slice thickness, 3.2 mm; slice gap, 0 mm; field of view, 360 mm; matrix size, 350 × 350; number of excitations, 0.8; imaging time, 58 s per phase; 8 phases of enhancement. Gadopentetate dimeglumine was administered at a dose of 15 ml and at a rate of 2.5 ml/s, followed by a 20-ml saline flush given with an automatic injector.

MRI Interpretation

MR images were analyzed by 2 specialized radiologists with 8 and 10 years of experience in MRI of the breast, who were blinded to the histopathology findings. The MRI descriptors described in the latest Breast Imaging Reporting and Data System (BI-RADS) MRI (5th edition) [13] were evaluated: maximum diameter; shape (round/oval, irregular); margin (circumscribed, non-circumscribed); dark internal septation (absent, present); initial enhancement increase (slow, moderate, rapid); kinetic curve pattern (persistent, plateau, washout); and delayed internal enhancement (homogeneous, heterogeneous, rim). The degree of lobulation (absent, weak, strong) and enhancing internal septation (absent, present) were evaluated according to reports regarding the differentiation of MBCs and FAs [8, 14]. The extent of lobulation was classified as strong (acute angle) or weak (obtuse angle) by referring to published criteria [14, 15]. In the process of imaging evaluation, we made a new observation: PMBCs with heterogeneous enhancement often were accompanied by local rim enhancement (more pronounced enhancement at the periphery than in the center of the local area of the tumor), whereas FAs presenting with heterogeneous enhancement had the opposite characteristic. Thus, in this study, we also evaluated delayed heterogeneous enhancement (with or without local rim enhancement). The region of interest (ROI) was placed manually on the area with the greatest degree of enhancement in the second phase, but ROI could not be placed in 6 PMBCs with rim enhancement because of a thin enhanced wall.

Statistical Analysis

The maximum diameter of the lesions was expressed as mean ± standard deviation. Comparison of the maximum diameters between PMBCs and FAs with T2-SHi was conducted with the independent sample t-test. Enumeration data, including shape, margin, enhancing internal septation, and local rim enhancement, were compared by use of Fisher's exact test. Dark internal septation was compared by using a χ^2 test. The nonparametric Mann-Whitney U test was used for the comparisons of lobulation, initial enhancement increase, kinetic curve pattern, and delayed enhancement pattern. A multivariate logistic regression analysis was conducted with significant variables in univariate analyses, except for local rim enhancement, to identify significant independent predictors for differentiating PMBCs from FAs with T2-SHi. $P < 0.05$ was considered statistically significant.

Results

The results of the univariate analysis of the DCE-MRI characteristics of PMBCs and FAs with T2-SHi are presented in table 1. The maximum diameter in PMBCs ranged from 1.0 to 5.9 cm and in FAs from 0.7 to 5.1 cm, and the mean maximum diameter of PMBCs was significantly greater than that of FAs (2.74 ± 1.15 cm vs. 1.74 ± 0.71 cm; $p < 0.001$). PMBCs also more often had an irregular shape, a non-circumscribed margin, and strong lobulation. Dark internal septation was present more commonly in FAs than in PMBCs, but enhancing internal septations were more common in PMBCs. The two kinds of lesions did not differ in frequency of initial enhancement increase or in kinetic curve pattern. Delayed rim enhancement was significantly more common with PMBCs than with FAs. For delayed-phase heterogeneous enhancement of PMBCs and FAs, local rim enhancement was detected more frequently in PMBCs.

The results of the multivariate analysis of DCE-MRI characteristics for the differentiation of PMBCs and FAs with T2-SHi are presented in table 2. Delayed enhancement pattern was the only significant independent predictor ($p = 0.007$). The odds ratios of heterogeneous and rim enhancement were 25.886 and 92.105, respectively.

Representative MR images of PMBCs and FAs with T2-SHi are shown in figures 1 and 2 and in figures 3 and 4, respectively.

Table 1. Results of the univariate analysis of the DCE-MRI characteristics of PMBCs and FAs with T2-SHi

	PMBCs	FAs	p
Size, cm	2.74 ± 1.15	1.74 ± 0.71	< 0.001
Shape			< 0.001
Oval	23 (65.7%)	68 (97.1%)	
Irregular	12 (34.3%)	2 (2.9%)	
Margin			< 0.001
Well-circumscribed	24 (68.6%)	69 (98.6%)	
Ill-circumscribed	11 (31.4%)	1 (1.4%)	
Lobulation			< 0.001
Absent	1 (2.9%)	22 (31.4%)	
Weak	17 (48.6%)	46 (65.7%)	
Strong	17 (48.6%)	2 (2.9%)	
Dark internal septation			0.001
Absent	23 (65.7%)	23 (32.9%)	
Present	12 (34.3%)	47 (67.1%)	
Enhancing internal septation			< 0.001
Absent	24 (2.9%)	69 (98.6%)	
Present	11 (31.4%)	1 (1.4%)	
Initial enhancement increasea			0.652
Slow	1 (3.5%)	3 (4.3%)	
Moderate	6 (20.7%)	17 (24.3%)	
Rapid	22 (75.9%)	50 (71.4%)	
Kinetic curve patterna			0.861
Persistent	21 (72.4%)	49 (70.0%)	
Plateau	7 (24.1%)	20 (28.6%)	
Washout	1 (3.5%)	1 (1.4%)	
Delayed enhancement pattern			< 0.001
Homogeneous	1 (2.9%)	42 (60.0%)	
Heterogeneous	17 (48.6%)	23 (32.9%)	
Rim	17 (48.6%)	5 (7.1%)	
Heterogeneous enhancement			< 0.001
Without local rim enhancement	2 (11.8%)	23 (82.1%)	
With local rim enhancement	15 (88.2%)	5 (17.9%)	

[a]The kinetic curve could not be generated because ROI could not be selected in 6 patients who had PMBCs with rim enhancement of a thin enhanced wall.
DCE = Dynamic contrast-enhanced, MRI = magnetic resonance imaging, PMBC = pure mucinous breast carcinoma, FA = fibroadenoma, T2-SHi = strong high-signal intensity on T2-weighted images, ROI = regions of interest.

Table 2. Results of the multivariate analysis of DCE-MRI characteristics for the differentiation of PMBCs and FAs with T2-SHi

Factor	Odds ratio	95% CI	p
Margin	14.723	0.393–551.653	0.146
Shape	2.454	0.146–41.183	0.533
Maximum diameter	1.708	0.612–4.767	0.307
No lobulation			0.142
Weak lobulation	4.344	0.405–46.542	0.225
Strong lobulation	22.967	0.992–531.908	0.051
Dark internal septation	0.739	0.136–4.001	0.725
Enhancing internal septation	5.771	0.231–144.311	0.286
Homogeneous enhancement			0.007
Heterogeneous enhancement	25.886	2.005–334.149	0.013
Rim enhancement	92.105	5.471–1,550.55	0.002

DCE = Dynamic contrast-enhanced, MRI = magnetic resonance imaging, PMBC = pure mucinous breast carcinoma, FA = fibroadenoma, T2-SHi = strong high-signal intensity on T2-weighted images, CI = confidence interval.

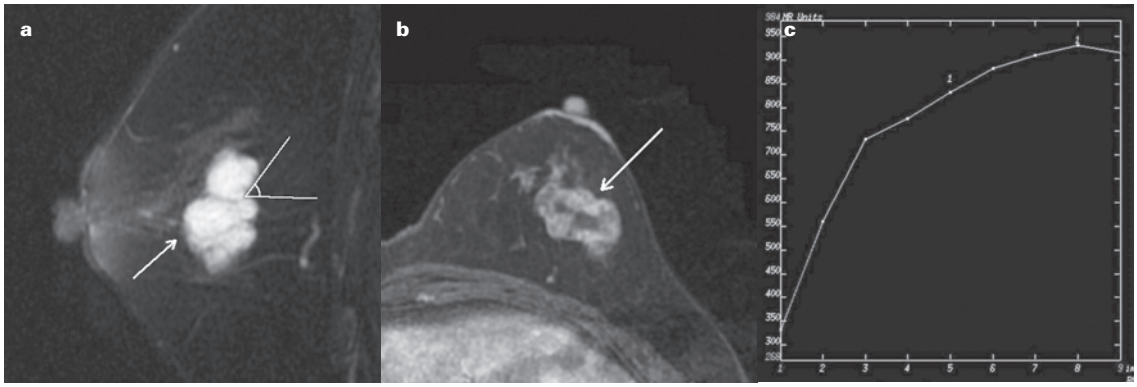

Fig. 1. A 46-year-old woman with a pure mucinous carcinoma in her left breast. The irregular mass (arrow) with strong high-signal intensity and strong lobulation (acute angle) on the sagittal fat-saturated T2-weighted images (**a**) shows rim enhancement (arrow) in the delayed phase (**b**) and rapid initial increase enhancement and a persistent enhancement pattern (**c**).

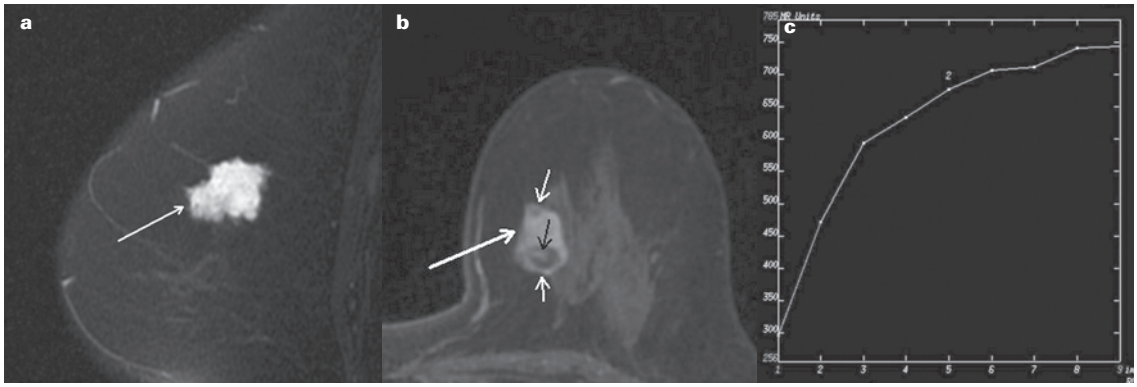

Fig. 2. A 59-year-old woman with a pure mucinous carcinoma in her left breast. The irregular mass (arrow) with irregular margin and strong high-signal intensity on the sagittal fat-saturated T2-weighted images (**a**) shows heterogeneous enhancement (long white arrow) with local rim enhancement (2 short white arrows) and enhancing internal septation (black arrow) in the delayed phase (**b**) and rapid initial increase enhancement and a persistent enhancement pattern (**c**).

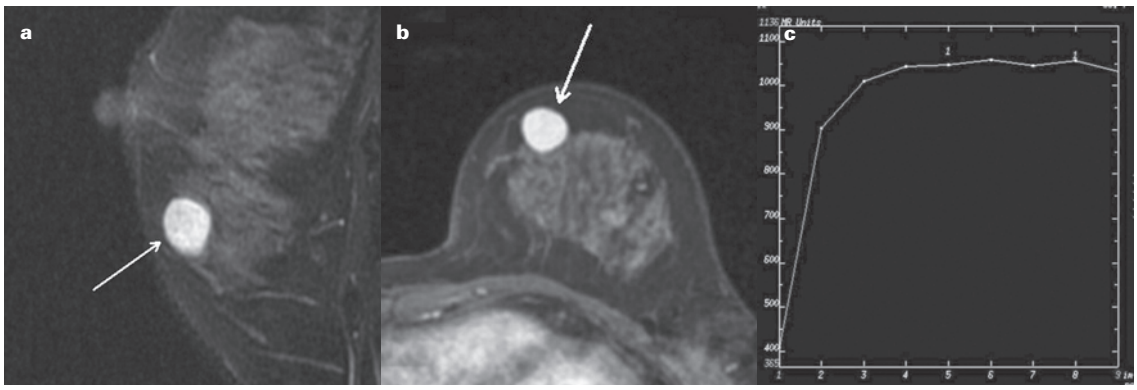

Fig. 3. A 42-year-old woman with FAs in her left breast. The oval mass (arrow) with circumscribed margin and strong high-signal intensity on the sagittal fat-saturated T2-weighted images (**a**) shows homogeneous enhancement (arrow) in the delayed phase (**b**) and rapid initial increase enhancement and a plateau enhancement pattern (**c**).

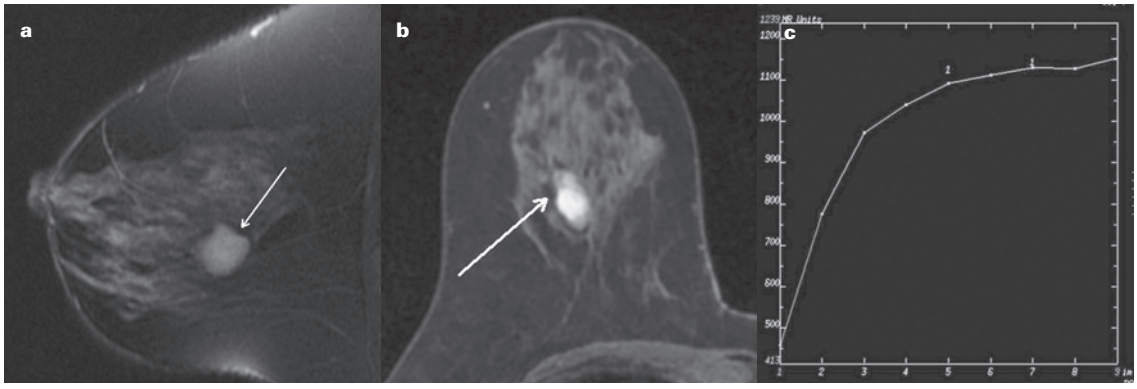

Fig. 4. A 52-year-old woman with FAs in her right breast. The oval mass (arrow) with circumscribed margin and strong high-signal intensity on the sagittal fat-saturated T2-weighted images (**a**) shows heterogeneous enhancement without local rim enhancement (arrow) in the delayed phase (**b**) and rapid initial increase enhancement and a persistent enhancement pattern (**c**).

Discussion

This study is the first we are aware of that has used DCE-MRI for differentiating PMBCs from FAs with T2-SHi. The results of the multivariate analysis revealed that delayed enhancement pattern was the most reliable predictive variable.

The enhancement pattern in the delayed phase of MRI has been considered to be more appropriate than that in the early phase because both the majority of PMBCs and FAs showed persistent enhancement [14]. The enhancement patterns of PMBCs were associated with histopathologic features and the time of acquisition: In the early phase, the pattern depended on the proportion and spatial distribution of tumor cell clusters and mucinous components; the areas of hypercellularity with high microvessel density had remarkable enhancement, whereas areas with abundant mucinous component lack blood supply and had inappreciable enhancement [16–18]. PMBCs predominantly had rim and heterogeneous enhancement in the early phase, corresponding to more proliferation of tumor cell clusters at the periphery than in the center, and the tumor cell clusters were irregularly distributed in mucin lakes. Less commonly, PMBCs had homogeneous or no appreciable enhancement in the early phase, corresponding to uniform distribution of a large number of tumor cells or very large amounts of mucin throughout the tumor. PMBCs showed centripetal progression over time because large amounts of mucus led to delayed diffusion of contrast material throughout the tumor. Thus, some tumors with rim enhancement in the early phase had heterogeneous enhancement in the delayed phase, with the enhancement difference between the tumor periphery and the center diminishing over time. A few tumors without enhancement in the early phase had heterogeneous enhancement in the delayed phase. Therefore, PMBCs more commonly had heterogeneous and rim enhancement than homogeneous and no appreciable enhancement in the delayed phase. Unlike PMBCs, FAs with T2-SHi mainly had delayed homogeneous enhancement on images from DCE-MRI. A previous study revealed that homogeneous enhancement in FAs resulted from uniformly distributed microvessels throughout the tumor [19]. Additionally, the difference in the distribution of contrast material between different regions within myxoid or edematous FAs gradually decreased and disappeared with time because myxoid or edematous changes of the stroma lead to both slow diffusion and delayed washout. However, in some cases, increased microvessels in regions that usually correspond to a single or several lobules in FAs cause heterogeneous enhancement. Concerning delayed-phase heterogeneous enhancement of PMBCs and FAs, local rim enhancement was more frequently detected in PMBCs than in FAs, which aided in the differentiation. We speculate that local rim enhancement detected in PMBCs with heterogeneous enhancement probably results from higher tumor cellularity at the periphery than in the center of the local area of the tumor. Rim enhancement is generally suggestive of malignancy, which correlates with more numerous microvessels at the periphery than in the center of the tumor, or necrosis or fibrosis in the center [20–22]. In a few cases, rim enhancement is detected also in benign lesions such as abscesses, inflammatory cysts, galactoceles, fat necrosis, and FA [14, 22, 23]. It has been hypothesized that relative hypovascularity in the center of an FA with rim enhancement is due to the presence of fibrosis or hyalinization [14]. In this study, 5 FAs with T2-SHi presenting with rim enhancement similar to that in PMBCs were found. However, these FAs had no other characteristics predictive of malignancy. Therefore, these FAs with T2-SHi could be accurately discriminated from PMBCs through integrated analysis of imaging characteristics.

We found that PMBCs had circumscribed as well as non-circumscribed margins, but non-circumscribed margins were more commonly seen in PMBCs than in FAs. Kryvenko et al. [24] classified PMBCs into paucicellular or cellular types, with a cutoff value of 60% mucin in the tumor, and considered that PMBCs originated from mucinous ductal carcinoma in situ, regardless of being paucicellular or cellular. Ductal overdistension and rupture of the basement membrane as a result of large amounts of mucin accumulated in the lumen lead to the extravasation of ductal contents, including mucin and tumor cells, which form paucicellular-type tumors with more indolent behavior. Breakage of the basement membrane by outpouchings of epithelia brings about tumor cells surrounded by mucin extravasating out of the lumen, which form the cellular-type tumors with more aggressive behavior. Furthermore, a higher nuclear grade and Ki-67 index, with cribriform/solid architecture, are more commonly seen in the cellular-type tumors [24]. Memis et al. [25] reported that the mammographic appearance of the margins of PMBCs varied with cellularity: Tumors with more mucin tended to have well-defined margins whereas tumors with large percentages of tumor cells tended to have more aggressive imaging characteristics. Therefore, we postulate that the different pathogeneses and histopathologic features of PMBCs account for the different appearances of margins.

In this study, dark internal septation was more frequently present in FAs with T2-SHi whereas enhancing internal septation was more frequently seen in PMBCs, a result that is consistent with the result of a previous study [8]: FAs with T2-SHi tended to have dark internal septation whereas MBCs tended to have enhancing internal septation. In another study, dark internal septation and enhancing internal septation differentiated MBCs from FAs with high specificity of 81.8% and 90.9%, respectively [14]. Dark internal septation both in PMBCs and FAs has been correlated with collagenous bands at histopathologic examination [16, 23], but enhancing internal septation has not been correlated with histopathologic findings.

This study found that the maximum diameter of PMBCs was significantly greater than that of FAs with T2-SHi. This finding is consistent with a report stating that the larger the tumor, the lower is the possibility of FAs [26], but it is inconsistent with a report of no significant difference in maximum diameter of MBCs and FAs [14]. In our study, irregular shape was seen in about one-third of the PMBCs but infrequently (about 3%) in FAs with T2-SHi, a finding that is inconsistent with the report of no significant difference in shape between MBCs and FAs [14]; the discrepancy in the results may be due to different sample selection because, in that

report, the MBC group included 24 PMBCs and 3 MMBCs similar to PMBCs, and the FA group included FAs with high or non-high signal intensity on T2-weighted imaging. With respect to lobulation, our study found that PMBCs had strong lobulation much more often than did FAs with T2-SHi. Similarly, Igarashi et al. [14] reported that strong lobulation was more frequently present in MBCs and weak lobulation was more frequently present in FAs. The extent of lobulation probably was helpful for differentiating PMBCs from FAs.

This study had limitations. First, small study populations from a single institution may cause large sampling errors; thus, further investigation with larger sample sizes is needed. Second, selection bias was inevitable because this was a retrospective study. Third, stratified analysis of PMBCs including paucicellular and cellular subtypes was not made. Fourth, many other conditions sharing T2-SHi with PMBC and FA, including mixed mucinous carcinoma, non-mucinous carcinomas, phyllodes tumor, and mesenchymal tumors were not taken into account.

Conclusions

In the DCE-MRI assessment of breast tumors, delayed enhancement pattern was the most reliable characteristic for differentiating PMBCs from FAs with T2-SHi. Rim enhancement or heterogeneous enhancement with local rim enhancement was more suggestive of PMBCs, whereas homogeneous enhancement or heterogeneous enhancement without local rim enhancement was more suggestive of FAs. Therefore, DCE-MRI may provide reliable evidence for the differentiation between PMBCs and FAs with T2-SHi.

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Disclosure Statement

All authors declare that they have no conflicts of interest.

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