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**MAJOR PAPER**

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## **Circumscribed Mass Lesions on Mammography: Dynamic Contrast-Enhanced MR Imaging to Differentiate Malignancy and Benignancy**

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**Purpose:** We evaluated the magnetic resonance (MR) features of breast lesions showing circumscribed mass on mammography to understand the characteristics that differentiate malignancy and benignancy.

**Materials and Methods:** Our institutional review board approved the study, and informed consent was waived. Using logistic regression analysis, we examined morphologic and kinetic MR imaging data of 90 breast lesions (43 malignant, 47 benign) that showed circumscribed mass on mammography.

**Results:** Features identified as having high odds for malignancy included: rim enhancement (odds ratio, 70.894; 95% confidence interval (CI), 7.525–667.938); heterogeneous enhancement (odds ratio, 10.839; 95% CI, 1.032–113.856); and washout dynamic pattern (odds ratio, 46.262; 95% CI, 3.716–575.901). Combinations of washout dynamic pattern and either rim or heterogeneous enhancement reflected excessively high prediction probability for malignancy ( $>0.95$ ), whereas combinations lacking washout dynamic pattern and with either homogeneous enhancement or dark internal septation revealed excessively low prediction probability for malignancy ( $<0.05$ ).

**Conclusion:** Breast cancers with circumscribed mass on mammography could be differentiated from benign masses using internal enhancement and the kinetic pattern of contrast-enhanced breast MR imaging.

**Keywords:** *breast neoplasm, mammography, MR imaging*

### **Introduction**

A breast lesion showing circumscribed mass on mammography is generally considered benign and classified into category 3 (or occasionally 4) according to the final assessment categories of the Breast Imaging Reporting and Data System (BI-RADS)-MAMMOGRAPHY.<sup>1</sup> Many of these lesions are benign, and category 3 lesions are managed with short-interval follow-up (6, 12, and 24 months from original examination) unless the findings increase in size or extent.<sup>1-3</sup> However, some breast cancers, such as invasive ductal carcinoma not otherwise specified (NOS), mucinous carcinoma, medullary carcinoma, or papillary carcinoma, are

also known to show circumscribed mass on mammography,<sup>4-9</sup> and thorough delineation of these malignancies is critical.

Magnetic resonance (MR) imaging of the breast is extremely sensitive for detecting breast cancer (83 to 99%), but specificity is reported at 37 to 97%.<sup>10-15</sup> This variation has been attributed to the presence of numerous morphologic and kinetic interpretation criteria for benign and malignant lesion features and the absence of standardized guidelines for acquisition and interpretation of MR images of the breast.<sup>16,17</sup> To enable clinicians to manage breast lesions adequately, the American College of Radiology has recently issued a standardized lexicon for analysis of breast MR findings in BI-RADS-MRI and provided assessment classifications for categorizing lesions by BI-RADS-MRI or mammography.<sup>18</sup> To differentiate benign and

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malignant breast lesions, Tozaki and colleagues reviewed MR features of 171 consecutive breast masses and proposed an interpretation model based on the kinetic and morphologic parameters of BI-RADS-MRI.<sup>19</sup> Their model showed 99% sensitivity, 89% specificity, 96% positive predictive value (PPV), and 98% negative predictive value (NPV). The features with the highest PPV for carcinoma were spiculated margin (100%) and heterogeneous enhancement following washout dynamic pattern in the smooth shape/margin group (100%). In addition, a lack of washout dynamic pattern in the smooth shape/margin group showed high NPV (100%).

One concern of clinicians is how to manage breast lesions that appear as circumscribed masses on mammography but that require further evaluation by breast MR imaging.<sup>2</sup> No precise reports have focused on these cases, and the Tozaki model, which is intended for all breast masses, may not work adequately in such special situations. This imaging evidence would help clinicians manage lesions of this type.

We sought to clarify the MR features of breast lesions showing circumscribed masses on mammography and to find the MR features, including morphology and kinetic pattern, that serve as discriminators between malignancy and benignancy.

## Materials and Methods

### Consent

Our institutional review board approved this retrospective study, and informed consent was waived.

### Patient population

A computer search of the radiological records from January 2001 through March 2005 in our institute revealed 421 patients with breast lesions showing circumscribed masses on mammography. Circumscribed mass was defined as a lesion with completely or partially circumscribed margin. Lesions with spiculated, microlobulated, or indistinct margins were excluded. Two radiologists (H.S. and T.K.) who did not participate in the MR evaluation selected cases with mammographical findings for evaluation and resolved classification disagreements by consensus. In 123 of the 421 patients, breast MR studies were performed for further examination of lesions. Indication for MR examination included final classification as category 4 with additional sonography, increased size on follow-up mammography, preoperative staging of breast cancer, nipple discharge, and uncertain results of aspi-

**Table 1.** Histology of 90 breast lesions showing circumscribed mass on mammography

Histology	Number
<b>Malignant</b>	
Invasive ductal carcinoma not otherwise specified (NOS)	24
Mucinous carcinoma	13
Medullary carcinoma	4
Intracystic papillary carcinoma	2
<b>Benign</b>	
Fibroadenoma	24
Intraductal papilloma	10
Benign phyllodes tumor	8
Fibrocystic change	4
Benign mucocele-like tumor	1

ration cytology. Eligible patients included those who underwent core needle biopsy, excisional biopsy, or surgical resection; 90 lesions (43 [48%] malignant, 47 [52%] benign) of 88 patients (women aged 13 to 81 years, mean 48 years) were enrolled in our study. Table 1 summarizes the histology. The average size of malignant lesions was 23.0 mm (range, 9.4 to 80.4 mm), of benign lesions, 31.7 mm (9.5 to 126.5 mm).

### MR imaging examination

All patients underwent MR examinations using a 1.5-tesla MR unit (Magnetom Symphony; Siemens, Erlangen, Germany) with commercially available breast coils within 2 weeks prior to core needle biopsy, excisional biopsy, or surgical resections. The patients lay in prone position during examination. Axial short-time inversion recovery T<sub>2</sub>-weighted images of the bilateral entire breast (repetition time/echo time/inversion time [TR/TE/TI], 8000/60/150 ms; echo train length, 11; field of vision [FOV], 300 × 300 mm; matrix, 198 × 256; thickness, 6 mm; gap, 1.5 mm; number of slices, 16; acquisition, 1; acquisition time, 169 s) were initially obtained. Subsequently, coronal T<sub>1</sub>-weighted images of the bilateral entire breast were obtained before and 5 times after the intravenous administration of contrast medium (dynamic MR study). Dynamic MR images were obtained sequentially at intervals of 60 to 300 s according to the method of Buadu and associates.<sup>20</sup> For acquisition of coronal T<sub>1</sub>-weighted images, a 3-dimensional, fat-suppressed, gradient-recalled echo, volumetric interpolated breath-hold examination sequence (3D-VIBE; TR/TE, 4.8/2 ms; flip angle, 15°; FOV, 150 × 300 mm; matrix, 218 × 512; thickness, 1 mm; acquisition, 1)

was used. For the dynamic MR study, gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) was administered intravenously at a rate of one mL/s (total dose of 0.1 mmol/kg) using an automatic power injector; flushing with 10 mL of saline followed.

### *Interpretation of the MR findings*

Working in consensus, 2 radiologists (T.O. and H.Y.) retrospectively reviewed the breast MR images. Both were fully qualified and had experience (T.O., 10 years; H.Y., 19 years) interpreting breast MR images. The MR findings were recorded according to the lexicon of BI-RADS-MRI.<sup>18</sup> Because each lesion in our study was detected as a “mass” on MR images, interpretation of the breast MR imaging findings was based on 5 points: shape of the mass (round, oval, lobular, or irregular); margin of the mass (smooth, irregular, or spiculated); internal mass enhancement (homogeneous, heterogeneous, rim enhancement, dark internal septation, enhancing internal septation, central enhancement, or no enhancement); initial rise of the time-signal intensity curve (TIC) on dynamic study (slow, medium, or rapid); and TIC pattern on the delayed phase of dynamic study (persistent, plateau, or washout). In evaluating the shape, margin, and internal enhancement of the mass, we used coronal contrast-enhanced 3D-VIBE MR images acquired at early phase (120 s after administration of contrast material) and axial and sagittal multi-planar reconstruction (MPR) images reconstructed from the coronal contrast-enhanced images according to the method of Liberman’s group.<sup>21</sup> The parameter, internal mass enhancement, had non-ordered categorical variables previously described in the literature;<sup>12,14</sup> however, when 2 or more features coexisted within a tumor, we selected a predominant finding. For the dynamic study, one author (T.O.) manually designated as the region of interest (ROI) the area within each tumor demonstrating the highest level of visual enhancement on coronal 3D-VIBE MR images of dynamic study (size of ROI, 6 to 30 mm<sup>2</sup>; mean, 20 mm<sup>2</sup>). The percentage of increase of signal intensity (%S-I) was defined as % S-I = [(signal intensity post – signal intensity pre) / signal intensity pre] × 100, and was used to construct the TIC. The initial rise in TIC was categorized into 3 patterns by the increase in signal intensity between the first 2 post-contrast images: ≤ 50% (slow pattern), > 50% and ≤ 100% (moderate), and more than 100% (rapid). The pattern of TIC on the delayed phase was categorized into 3 types by the signal intensity time courses in the last 3 post-contrast images: increasing signal intensity

throughout the dynamic period (persistent pattern); stabilized enhancement without change in signal intensity between the initial and subsequent post-contrast images (plateau pattern); and abrupt decline in signal intensity after the initial post-contrast images (washout pattern). The initial rise patterns were classified according to the definition of Fischer and associates,<sup>22</sup> and the TIC patterns on the delayed phase were classified according to that of Kuhl’s group.<sup>11</sup>

### *Data analysis*

We used chi-square or Fisher’s exact test to calculate the differences between malignant and benign lesions in proportions of each MR finding present. For enhancing lesions, we performed logistic regression analysis by the step-wise method to select statistically significant MR findings associated with malignancy, and we calculated the odds ratio of each MR finding. In addition, we calculated the probability of malignancy associated with each combination of MR imaging findings. We also tested the interpretation model of Tozaki’s group using combinations of MR features showing 100% PPV (spiculated margin or heterogeneous enhancement following washout dynamic pattern in the smooth shape/margin group) and 100% NPV (a lack of washout dynamic pattern in the smooth shape/margin group) in their study.  $P < 0.05$  was considered statistically significant. The statistical calculation was performed with the Dr. SPSS II for Windows (SPSS Japan Inc., Tokyo, Japan).

## **Results**

### *MR features of breast lesions*

Table 2 shows the frequency of MR findings in all 90 lesions and the  $P$ -values for lesion differentiation between descriptors of benignancy and those of malignancy on chi-square or Fisher’s exact test. With respect to internal mass enhancement, rim (22/27, 81%) and heterogeneous enhancement (18/26, 69%) were more commonly seen in malignant lesions, and dark internal septation (22/23, 96%), homogeneous enhancement (7/8, 88%), and no enhancement (5/6, 83%) were primary findings in benign lesions. With respect to the TIC pattern on the delayed phase, a washout dynamic pattern (21/22, 95%) was seen primarily in malignant lesions, and a persistent pattern (23/33, 70%) was more common in benign lesions. Statistically significant differences were found between benignancy and malignancy in internal mass enhancement ( $P < 0.001$ ) and TIC pattern on delayed phase ( $P < 0.001$ ). Table 3 shows the results of step-wise logis-

**Table 2.** Magnetic resonance (MR) imaging features of 90 breast lesions showing circumscribed mass on mammography

Feature	Total	Benign	Malignant	<i>P</i> -value
Shape of mass				0.423
Round	27	14	13	
Oval	22	14	8	
Lobular	41	19	22	
Irregular	0	0	0	
Margin of mass				0.205
Smooth	72	40	32	
Irregular	18	7	11	
Spiculated	0	0	0	
Internal mass enhancement				<0.001
Homogenous	8	7	1	
Heterogeneous	26	8	18	
Rim enhancement	27	5	22	
Dark internal septation	23	22	1	
Enhancing internal septation	0	0	0	
Central enhancement	0	0	0	
No enhancement	6	5	1	
Initial rise of time-signal intensity curve (TIC)*				0.144
Slow	8	6	2	
Moderate	7	5	2	
Rapid	69	31	38	
TIC pattern on delayed phase*				<0.001
Persistent	33	23	10	
Plateau	29	18	11	
Washout	22	1	21	

\* Evaluation of 84 enhancing breast lesions.

**Table 3.** Results of step-wise logistic regression analysis of magnetic resonance (MR) features of 84 enhancing breast lesions

Magnetic resonance feature	<i>P</i> -value	Odds ratio	Exp(B) 95%	
			Lower level	Upper level
Internal mass enhancement*	<0.001			
Heterogeneous	0.047	10.839	1.032	113.856
Rim enhancement	<0.001	70.894	7.525	667.938
Homogeneous	0.979	1.049	0.031	35.746
TIC pattern on delayed phase**	0.008			
Washout	0.003	46.242	3.716	575.901
Plateau	0.950	1.047	0.248	4.418

\* "Dark internal septation" was used as the baseline.

\*\* "Persistent" was used as the baseline.

TIC: time-signal intensity curve

Exp(B) 95%: 95% confidence interval of odds ratio

tic regression analysis. Internal mass enhancement ( $P < 0.001$ ) and TIC pattern on delayed phase ( $P = 0.008$ ) were statistically significantly different be-

tween malignancy and benignancy. Rim (odds ratio, 70.894; 95% confidence interval [CI], 7.525 to 667.938) and heterogeneous enhancement (odds ra-

tio, 10.839; 95% CI, 1.032–113.856) on internal mass enhancement displayed high odds ratios for malignancy. The washout dynamic pattern (odds ratio, 46.262; 95% CI, 3.716 to 575.901) on TIC on delayed phase also displayed a high odds ratio for malignancy.

#### *Calculation of prediction probability for malignancy*

Prediction probabilities for malignancy of combined MR features were calculated using the results of step-wise logistic regression analysis (Table 4). Lesions with rim enhancement and a washout dynamic pattern (0.99320) (Fig. 1) or with heterogeneous enhancement and a washout dynamic pattern (0.95714) displayed excessively high prediction probabilities for malignancy. Lesions with rim enhancement and a plateaued dynamic pattern (0.76783), with rim enhancement and persistent dynamic pattern (0.75947) (Fig. 2), with homogeneous enhancement and a washout dynamic pattern (0.68362), with heterogeneous enhancement and plateaued dynamic pattern (0.33582), or with heterogeneous enhancement and a persistent dynamic pattern (0.32558) displayed moderate prediction probability for malignancy. Lesions with dark internal septation and persistent dynamic pattern (0.04264) (Fig. 3), with dark internal septation and plateaued pattern (0.04457), with homogeneous enhancement and a persistent dynamic pattern (0.04462), or with homogeneous enhancement and plateaued dynamic pattern (0.04664) displayed excessively low prediction probability for malignancy. After applying the interpretation model of

Tozaki's group to our results, the PPV of heterogeneous enhancement following washout dynamic pattern in the smooth margin group was 93% (14/15), whereas NPV of a lack of washout dynamic pattern in the smooth margin group was 68% (39/57).

#### **Discussion**

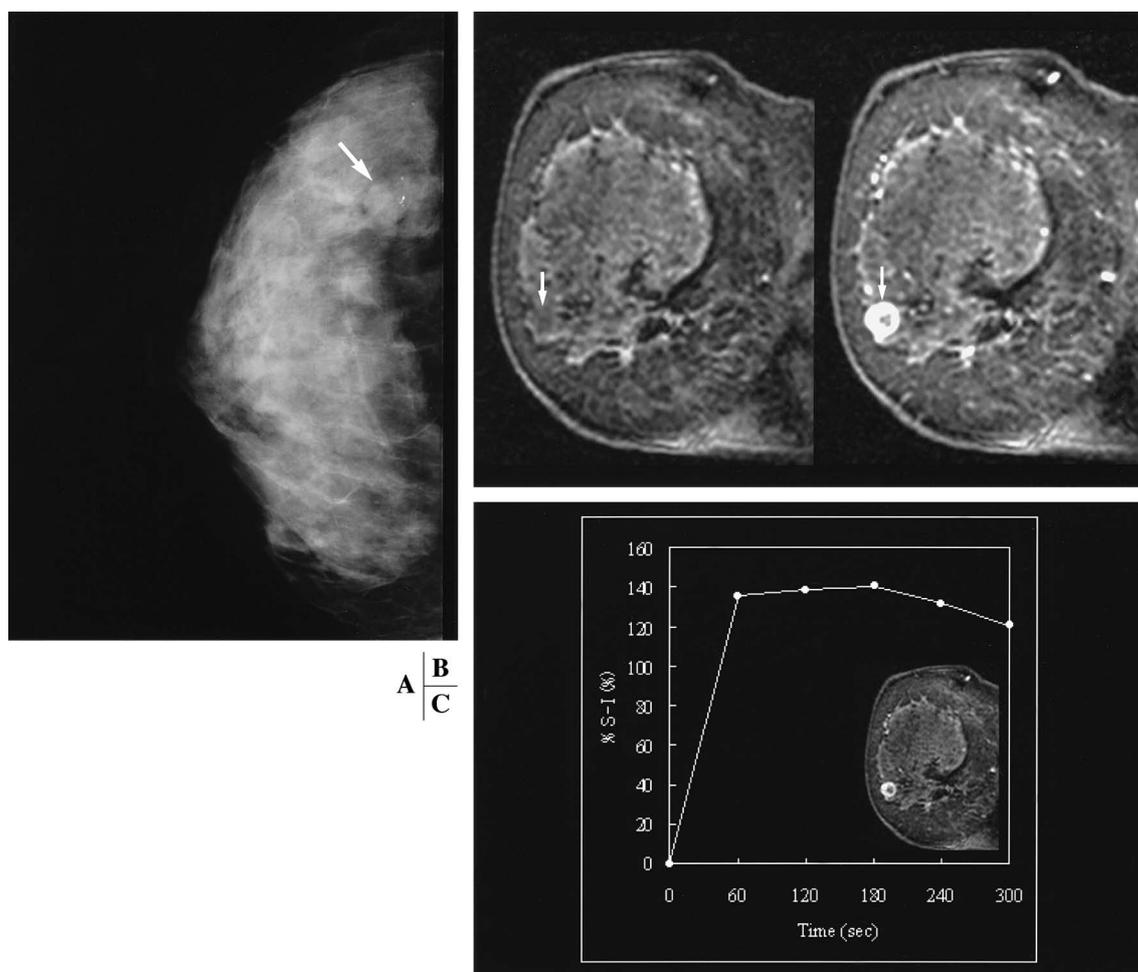
This report has clarified the MR features as assessed by logistic regression analysis of breast lesions showing circumscribed mass on mammography and the statistically significant MR features that may be used to differentiate malignancy and benignancy. In the step-wise logistic regression analysis, internal mass enhancement and a TIC pattern on delayed phase were statistically significantly different between malignant and benign masses. Moreover, rim enhancement or heterogeneity on internal mass enhancement and a washout dynamic pattern on TIC on delayed phase were considered features suspicious for malignancy because they had odds ratios higher than those of the other MR findings. These results were consistent with those of past reports on dynamic MR imaging of invasive breast cancer.<sup>5,11,12,14,21,23–25</sup> Combinations of washout dynamic pattern and either rim or heterogeneous enhancement showed excessively high prediction probability for malignancy (>0.95), whereas combinations of lacking washout dynamic pattern with either homogeneous enhancement or dark internal septation revealed excessively low prediction probability for malignancy (<0.05). On the other hand, neither shape nor margin was significantly different between the malignant and benign lesions, and this was considered to result from the selection bias of the present study, that is, the collection of breast lesions with circumscribed margin on mammography.

With respect to internal mass enhancement, it is generally believed that inhomogeneous enhancements, such as rim or heterogeneous enhancement, are MR features of breast cancer. We observed rim or heterogeneous enhancement in 93% of malignancies, and these MR findings were considered to be indicative of malignancy with high odds ratio on step-wise logistic regression analysis (rim enhancement, 70.894; heterogeneous, 10.839). In particular, early rim enhancement has been known to be a predictive feature for breast malignancy and may occur in as many as 21 to 67% of breast malignancies.<sup>5,12,14,24–27</sup> Rim enhancement is explained histopathologically by a necrotic or fibrotic zone in the tumor center and angiogenic activity in the viable tumor tissue at the periphery of the tumor.<sup>26,27</sup>

**Table 4.** Prediction probabilities for malignancy calculated using the results of step-wise logistic regression analysis

Internal mass enhancement on delayed phase	TIC pattern	Prediction probability for malignancy
Rim enhancement	Washout	0.99320
Heterogeneous	Washout	0.95714
Rim enhancement	Plateau	0.76783
Rim enhancement	Persistent	0.75947
Homogeneous	Washout	0.68362
Heterogeneous	Plateau	0.33582
Heterogeneous	Persistent	0.32558
Homogeneous	Plateau	0.04664
Homogeneous	Persistent	0.04462
Dark internal septation	Plateau	0.04457
Dark internal septation	Persistent	0.04264

TIC: time-signal intensity curve

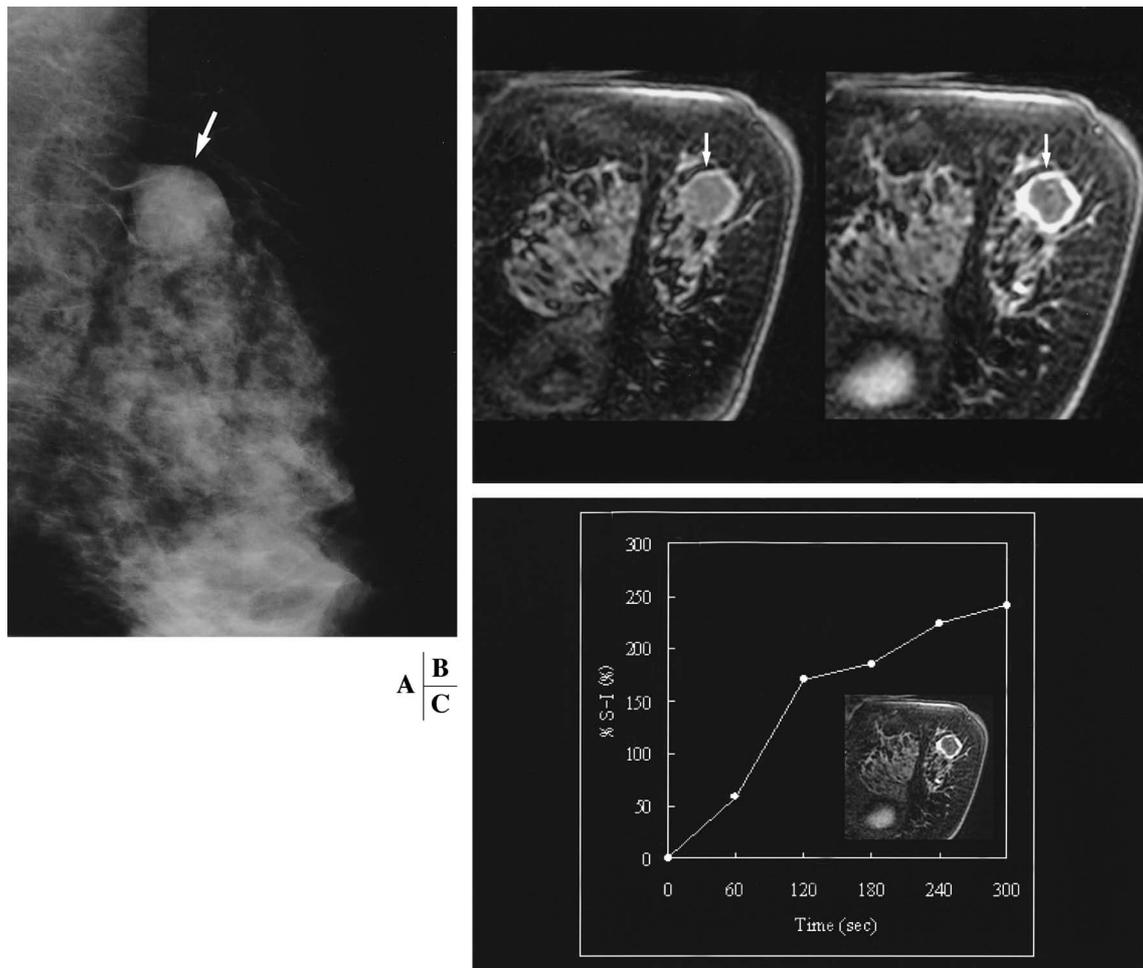


**Fig. 1.** Images obtained from a 51-year-old woman with invasive ductal carcinoma not otherwise specified (NOS) of the right breast. **A:** A craniocaudal mammogram shows a lobular mass with circumscribed margin (white arrow). **B:** On pre- (left sided image) and post-contrast enhancement of the second dynamic phase (right) coronal, 3-dimensional, fat-suppressed, gradient-recalled echo, volumetric interpolated breath-hold examination sequence (3D-VIBE) magnetic resonance (MR) images (repetition time/echo time [TR/TE], 20/6 ms; flip angle, 30°), the right breast mass showed rim enhancement (small white arrows). **C:** The time-signal intensity curve (TIC) obtained from the region of interest (ROI) showed a washout pattern.

In contrast, it is generally believed that dark internal septation on a contrast-enhanced MR image is a feature of breast benignity,<sup>12,14,21</sup> and we observed dark internal septation in 22/47 (47%) of benignities and in only one of 43 malignancies. In past reports, dark internal septation was reported in 27 to 64% of fibroadenomas or benign phyllodes tumors<sup>28,29</sup> and corresponded histopathologically to a dense collagen band separating rounded subunits that consisted of epithelium-lined ducts surrounded by mesenchymal stroma.<sup>29,30</sup> In our study, 21 of 23 lesions showing dark internal septation were fibroadenomas or benign phyllodes tumors.

Several studies have indicated that enhancement kinetics in the delayed post-contrast periods, as represented by the TIC, differ significantly between

benignancy and malignancy and therefore may aid in differential diagnosis.<sup>10,11</sup> Breast malignancies usually exhibit stabilized enhancement without change in signal intensity between the initial and subsequent post-contrast images (plateau dynamic pattern) or abrupt decline in signal intensity after the initial post-contrast images (washout dynamic pattern). In particular, a washout dynamic pattern has been noted to be fairly specific for malignancy and may occur in as many as 38 to 85% of breast cancers.<sup>11,14,20,21,26</sup> We observed a washout dynamic pattern in 21/43 (49%) of malignancies and only one case of benignancy; washout dynamic pattern was considered an MR feature of malignancy, with a high odds ratio (46.262) on logistic regression analysis as well as in results of past reports. We



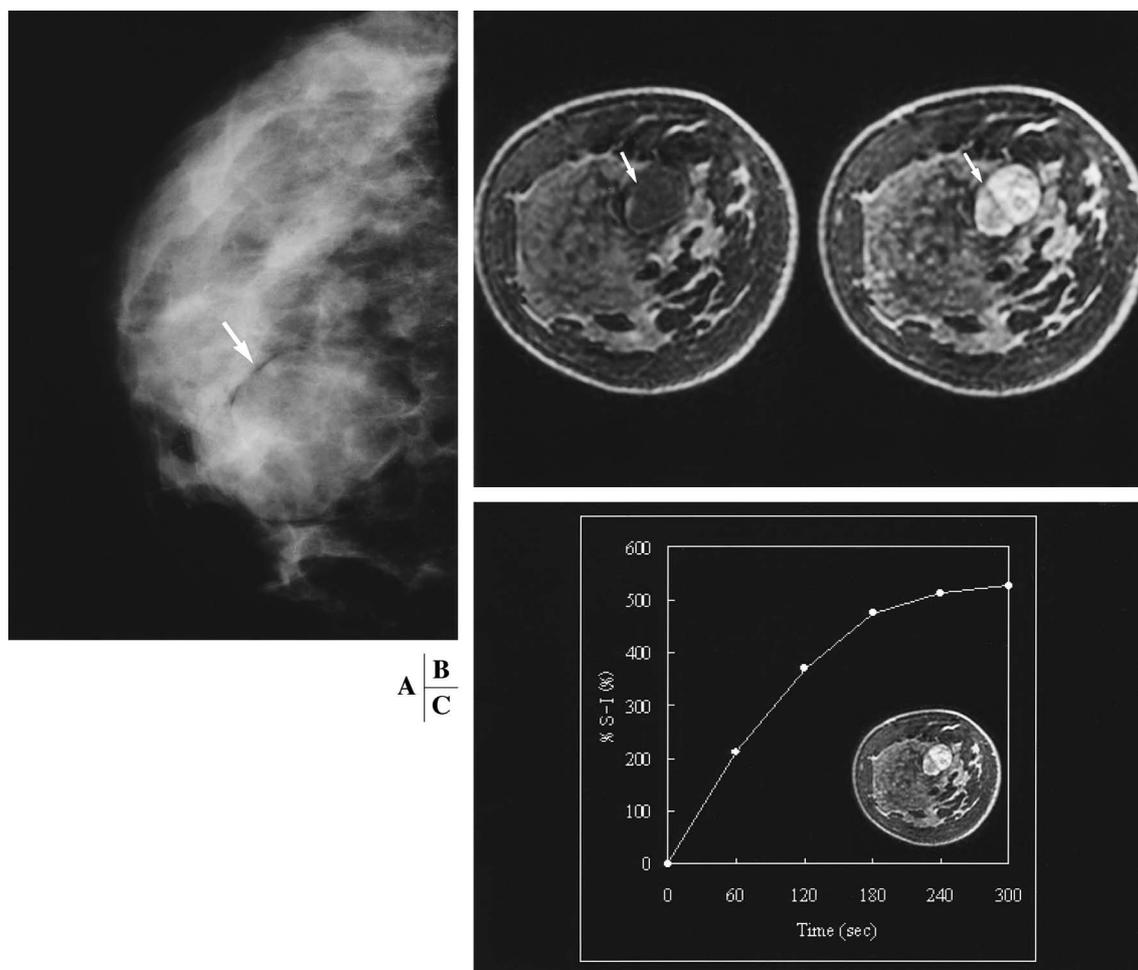
**Fig. 2.** Images obtained from a 40-year-old woman with intracystic papillary carcinoma of the left breast. **A:** A mediolateral oblique mammogram of the left breast showed a round mass with a partially circumscribed and partially obscure margin (white arrow). **B:** On pre- (left) and post-contrast (right sided image) enhanced coronal, 3-dimensional, fat-suppressed, gradient-recalled echo, volumetric interpolated breath-hold examination sequence (3D-VIBE) magnetic resonance (MR) images (repetition time/echo time [TR/TE], 20/6 ms; flip angle, 30°), the left breast mass showed rim enhancement (small white arrows). **C:** The time-signal intensity curve (TIC) obtained from the region of interest (ROI) showed a persistent pattern.

speculate that the relatively low frequency of wash-out dynamic pattern compared with results of previous studies was attributable to our specific patient population. In our study, a significant proportion of malignancy were mucinous carcinomas (13/43), 12 of which showed persistent dynamic pattern. Our unique study population may have influenced the low frequency of washout dynamic pattern.

In contrast, benign lesions have been reported to exhibit a steadily progressive signal intensity (persistent dynamic pattern), observed in 23 of 47 benignities (49%). In past reports, however, 5 to 14% of breast cancers (tumors rich in stroma, such as breast cancer with a large fibrous component, or mucinous carcinoma) exhibited a persistent dynamic pattern,<sup>10,11,13,20,31</sup> which was thought to reflect the

gradual movement of contrast medium to the stroma.<sup>20,31</sup> Thus, malignancies showing persistent dynamic pattern on the kinetic curve may be diagnosed as benignity by kinetic assessment alone. In our study, 10 of 43 malignancies (23%) showed a persistent pattern.

A lack of enhancement on post-contrast MR imaging is generally considered indicative of benignity,<sup>11,14,29</sup> and non-enhancing lesions, such as cysts or hyalinized non-enhancing fibroadenomas, are described as examples of benign lesions (category 2) in BI-RADS-MRI. One malignancy in our study, a mucinous carcinoma, showed no enhancement. It has been reported that some breast malignancies may show no enhancement,<sup>32</sup> and a case of mucinous carcinoma was reported that showed no en-



**Fig. 3.** Images obtained from a 28-year-old woman with fibroadenoma of the right breast. **A:** A craniocaudal mammogram of the right breast showed a lobular mass with a partially circumscribed and partially obscure margin (white arrow). **B:** On pre- (left) and post-contrast (right) enhanced coronal, 3-dimensional, fat-suppressed, gradient-recalled echo, volumetric interpolated breath-hold examination sequence (3D-VIBE) magnetic resonance (MR) images (repetition time/echo time [TR/TE], 20/6 ms; flip angle, 30°), the right breast mass showed dark internal septation (small white arrows). **C:** The time-signal intensity curve (TIC) obtained from the region of interest (ROI) showed a persistent pattern.

hancement on contrast-enhanced MR imaging.<sup>33</sup> Although a breast mass with no enhancement should be classified into category 2, it is important to keep in mind that some malignancies may show no enhancement.

In comparison to findings reported by Tozaki's group, ours included no lesion with spiculated margin, and NPV of lacking washout dynamic pattern in the smooth margin group was 68% (39/57). Moreover, the PPV of heterogeneous internal enhancement following washout dynamic pattern in the smooth margin group in our study was 93% (14/15) because there was a case of papilloma. The relatively low NPV of lacking washout dynamic pattern in the smooth margin group probably resulted from the unique composition of our study

group, which included a significant fraction of breast cancers showing this pattern (18/43; 12 mucinous carcinomas, 6 non-mucinous carcinomas). Thus, in a special situation, such as the case of a circumscribed mass on mammography, the interpretation model that is intended for all breast masses requiring MR examination may not always work correctly.

### Conclusion

Breast cancers showing a circumscribed mass on mammography could be differentiated from benign tumors by internal enhancement and the kinetic pattern of contrast-enhanced breast MR imaging. In particular, combinations of washout dynamic

pattern and either rim or heterogeneous internal enhancement showed excessively high prediction probability for malignancy ( $>0.95$ ), whereas combinations of lacking washout dynamic pattern and either homogeneous internal enhancement or dark internal septation revealed excessively low prediction probability for malignancy ( $<0.05$ ).

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