# Dynamic contrast-enhanced MR imaging in screening detected microcalcification lesions of the breast: is there any value?

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**Abstract**

*Purpose* To prospectively evaluate whether dynamic contrast-enhanced magnetic resonance (MR) imaging findings can help predict the presence of malignancy when screening detected microcalcification lesions, and its contribution to patient management of stereotactic vacuum-assisted breast biopsy (SVAB).

*Materials and methods* Dynamic contrast-enhanced breast MR imaging was performed when screening 100 detected microcalcification lesions not visualized by ultrasonography with 11-gauge SVAB. Definitive surgery was performed on all patients with the biopsy resulting in the diagnosis of breast cancer or atypical ductal hyperplasia (ADH). Positive predictive values (PPVs) and negative predictive values (NPVs) were calculated on the basis of a BI-RADS (Breast Imaging Reporting and Data System) category and the absence or presence of contrast uptake in the area of microcalcification.

*Results* The BI-RADS mammography category correlated with the diagnosis of breast cancer (ADH excluded): category 3 = 7% (4/55); category 4 = 48% (13/27); category 5 = 94% (17/18). After dynamic contrast-enhanced MR imaging, three of four malignancies with BI-RADS mammography category 3 were diagnosed as true positive. Therefore, the PPV of BI-RADS mammography category 3 with MR imaging was 1.8% (1/55). The PPV of contrast uptake of MR imaging was 86% (32/37), significantly higher than the 67% (30/45) PPV of BI-RADS mammography 4 and 5 (*P* = 0.033). The NPV of BI-RADS mammography 3 was 93% (51/55) versus 97% (61/63) NPV of MR imaging (*P* = 0.167).

*Conclusion* In the evaluation of screening detected microcalcification lesions, dynamic contrast-enhanced breast MR imaging provides additional information with high PPV and NPV, and may therefore offer an alternative to SVAB for women who do not want to undergo SVAB with equivocal findings following full diagnostic mammographic assessment, but breast MR imaging with imperfect PPV and NPV cannot replace SVAB.

*Clinical relevance* Dynamic contrast-enhanced breast MR imaging can demonstrate malignant microcalcifications detected by screening mammography and can be recommended in the evaluation of equivocal microcalcifications prior to SVAB.

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## Introduction

The extension of screening mammography has resulted in a decreased number of patients who die of breast

cancer because mammography is sensitive for the detection of clinically occult breast cancer [1, 2]. Although clinically occult breast cancers detected by mammography may also represent small invasive carcinoma, abnormal screening mammographic findings are the most common presentation of ductal carcinoma in situ (DCIS) and DCIS usually appears as clustered microcalcification [3]; however, specificity ranges from 10% to only 35% [4]. To our knowledge, there are no explicit guidelines for the categorization of clustered microcalcifications, although the Breast Imaging Reporting and Data System (BI-RADS) is intended to standardize the terminology in mammographic reports, the assessment of the findings, and recommend the action to be taken [5]. Concern that many concerning microcalcifications may be malignant has led to recommendations that all concerning microcalcifications require histologic evaluation [6]; however, 20–25% of patients who underwent biopsy had malignancy among lesions classified as BI-RADS 4 (suspicious abnormality) [7–9]. Although short-term mammographic follow-up is often recommended for probably benign lesions (BI-RADS 3) [5], the positive predictive value (PPV) of BI-RADS 3 lesions using stereotactic vacuum-assisted breast biopsy (SVAB) is 2.7–4.5%, and especially in BI-RADS category 3 microcalcifications, 7% were positive [7, 10, 11]. However, the estimated probability of malignancy in BI-RADS 3 lesions is lower than 2% [12, 13]. A recent study suggested that non-palpable lesions with microcalcifications categorized as BI-RADS 3 should undergo a biopsy procedure until a more reliable system for the description and classification of microcalcifications is available [14]. Another study suggested that BI-RADS 3 microcalcifications with risk factors may undergo SVAB [15]. SVAB is of sufficient sensitivity and specificity to replace surgical biopsy and offers valuable advantages for the evaluation of small concerning lesions and microcalcifications [10].

Magnetic resonance (MR) imaging of the breast provides tissue vascularity information that is not available from mammography and many breast cancers have neovascularity that causes enhancement of the tumor after the injection of intravenous contrast material [16]. Although breast MR imaging has demonstrated variable specificity, the sensitivity for the demonstration of invasive ductal carcinoma has approached 100% [17]. Moreover, the role of breast MR imaging in detecting microcalcifications remains a debated issue [18–22].

Therefore, the purpose of our study was to prospectively determine the frequency of malignancy in BI-RADS 3 microcalcifications using SVAB, to evaluate whether dynamic contrast-enhanced MR imaging findings can help predict the presence of malignancy in screening that detected microcalcification lesions and its contribution to patient management of SVAB.

## Materials and methods

### Patient population

Entrance criteria were women undergoing the screening of detected microcalcification lesions diagnosed as BI-RADS 3, 4, and 5 after additional mammographic and ultrasonographic work-up. In our institution, all lesions, including ill-defined masses, visible on ultrasonography (US) undergo US-guided core needle biopsy. Therefore, SVAB was performed on microcalcification lesions without mass in this study. Consecutive patients at our institution were recruited from October 2002 through December 2005. Women had to (a) agree to undergo dynamic contrast-enhanced MR imaging of the breast and SVAB according to an institutional review board-approved protocol and (b) provide informed consent. Women who were unable to provide consent or undergo MR imaging because of a pacemaker, claustrophobia, or a non-titanium metallic clip were excluded, as were patients with a blood coagulation disorder, current treatment with anticoagulation, or unable to cooperate with the SVAB procedure. Although existing data support that BI-RADS 3, probably benign lesions, can be identified and safety managed with short-term follow-up mammography [12, 13] and BI-RADS recommends 6-month follow-up imaging rather than immediate biopsy for category 3 probably benign lesions [5], the management of BI-RADS 3 lesions continues to be debated [14, 15, 23, 24]. Moreover, BI-RADS states that most approaches to category 3 probably benign lesions are intuitive [5]. We therefore recommended that women with BI-RADS 3 microcalcifications were assessed by dynamic contrast-enhanced MR imaging and SVAB in this study period.

### Imaging protocols

#### Mammography protocol and interpretation

Bilateral digital mammography was performed (Senographe 2000D unit; GE Medical Systems, Milwaukee, WI, USA) and included routine craniocaudal and mediolateral oblique views of the breasts

and spot-magnification views over the area of microcalcification. The digital mammograms were independently double-read using BI-RADS assessment categories [5] by two radiologists with 8–12 years of experience in mammography. Readers also rated breast density according to the standard BI-RADS scale (extremely dense, heterogeneously dense, scattered fibroglandular densities, and almost completely fat). If different BI-RADS assessment categories and BI-RADS breast density scales were assigned by the two readers, consensus was reached by discussion. Microcalcification lesions were classified according to BI-RADS descriptors for mammographic features including calcification morphology (punctate, amorphous, pleomorphic, linear) and distribution (diffuse, regional, clustered, segmental, linear) [5].

*Breast US protocol and interpretation*

Bilateral whole-breast US was performed with the knowledge of clinical and mammographic findings prior to MR imaging and SVAB. US was performed by one of five US technologists with 2–20 years of experience in breast US. Using a linear-array broadband transducer with a center frequency of 10–12 MHz, US was performed and supplemented with a linear-array transducer with a center frequency of 7.5 MHz as needed to penetrate larger breasts (LOGIQ 9 unit; GE Medical Systems, Milwaukee, WI, USA, or Aplio unit; TOSHIBA, Tokyo, Japan, or ProSound SSD-6500 unit; ALOKA, Tokyo, Japan). US findings were interpreted by one radiologist who has extensive experience in mammography, US and MR imaging of the breast, and one of five US technologists who did the breast US examination. Based on the US findings, one radiologist, who performs more than 400 US-guided core needle breast biopsy procedures annually, verified the SVAB indication; that is to say, lesions for which an US-guided core needle breast biopsy was possible were eliminated from this study.

*Breast MR imaging protocol and interpretation*

Magnetic resonance imaging examinations were performed with the patients in the prone position. The instrument was a 1.5T commercially available system (Gyroscan Intera; Philips Medical Systems, Best, The Netherlands) with double breast-surface coils. Our image protocol includes a localizing sequence followed by sagittal fast-spin echo T2-weighted imaging (TR/TE, 5056/90; ETL, 15; matrix, 158 × 320) with fat suppression (SPIR; Spectral Presaturation Inversion

Recovery) of the affected breast. Other parameters were field-of-view, 18 cm; section thickness, 4 mm; interslice gaps, 0.8 mm. This examination was followed by dynamic study of the affected breast, consisting of serial imaging of a three-dimensional sagittal turbo-field echo T1-weighted sequence (TR/TE, 11/5.4; flip angle, 20; matrix, 143 × 256) with fat suppression (ProSet; Principle of Selective Excitation Technique). The parameters were field-of-view, 18 cm; section thickness, 2 mm; interslice gap, -1 mm. Gadopentetate dimeglumine (Magnevist; Nihon Schering, Osaka, Japan) was administered as a bolus intravenous injection (2 mL/s) at a dose of 0.1 mmol/kg body weight. This was followed by a 20-mL saline solution flush. For dynamic study, we acquired one pre- and three post-enhancement scans; the scan time was 2 min per scan.

Each MR examination was independently double-read using BI-RADS-MRI lexicon [5] by two radiologists with 5–6 years of experience in breast MR imaging. Any contrast enhancement in the area of intermediate microcalcification was considered positive. The absence of contrast enhancement in the area of intermediate microcalcification was considered negative. Two radiologists decided whether it was positive or negative.

Morphology [5] and kinetics [5] at MR imaging were evaluated for all enhancing microcalcification lesions.

SVAB protocol

We performed SVAB with the patients prone on a digital stereotactic table (LoRad DSM; Hologic, Danbury, CT, USA) with a vacuum-assisted biopsy device using 11-gauge probes (Mammotome; Biopsys Medical/Ethicon Endo-Surgery, Cincinnati, OH, USA). One radiologist with 1 year of prior experience SVAB performed the biopsy. Specimen radiography was performed routinely on all microcalcifications. If no microcalcifications were observed in the specimen, biopsy was considered to be not representative and another biopsy was recommended. Complete or partial removal of the microcalcifications was assessed in all cases on two view full field mammograms immediately. If microcalcification had been removed completely or almost completely, clips were placed through the 11-gauge probe to identify the SVAB site for subsequent surgical excision [25]. Moreover, if correct removal could not be verified on the check-up mammograms, we judged that SVAB was unsuccessful and re-biopsy was recommended. The histopathologic result was correlated with the mammographic findings by both the radiologist and pathologist in all cases.

*Histologic diagnosis*

Histologic diagnoses were determined by one pathologist with 16 years of experience with breast histology. The histologic findings were classified into three groups as malignant, high risk, or benign. Malignant lesions included invasive carcinoma and DCIS. The grade of DCIS was scored as low, intermediate, or high. We considered atypical ductal hyperplasia (ADH) and atypical cells to be high-risk lesions, for which the associated presence of carcinoma can be underestimated with SVAB. Lesions that were not categorized as histologically malignant or high risk were classified as benign.

Management protocol

In our institution, we use SVAB in lieu of an initial excisional biopsy. If malignancy was found at SVAB, the surgeon performed a therapeutic operation, including axillary surgery if indicated. If SVAB yielded high-risk lesions such as ADH, the surgeon performed surgical excision. If a benign lesion was found at SVAB, the patient was scheduled for repeat mammography of the ipsilateral breast at 3 and 6 months and annual screening mammography were recommended thereafter. If there was calcification progression at post-SVAB mammographic follow-up, delayed repeat SVAB was recommended.

Analysis

For histologic analysis, we grouped the microcalcifications into two main categories, benign and malignant, with the latter category including invasive carcinoma and DCIS, not including ADH and atypical cells as high-risk lesions.

For mammography, malignant lesion was considered to be diagnosed successfully (true positive) if it appeared to be suspicious for or highly suggestive of malignancy classified as BI-RADS categories 4 or 5. Calcifications considered probably benign, assigned as BI-RADS category 3 that proved to be malignant at SVAB or surgery, were classified as false-negative mammography findings.

For dynamic contrasted-enhanced breast MR imaging, a malignant lesion was considered to be diagnosed successfully (true positive) if it showed contrast uptake in the area of microcalcification. The absence of contrast uptake in the area of microcalcification that proved to be malignant at SVAB or surgery was classified as false-negative MR imaging findings.

We calculated the PPVs and NPVs of the BI-RADS mammography category and the absence or presence of contrast uptake in the area of microcalcification for diagnosing microcalcification as benign or malignant using $2 \times 2$ contingency tables. Chi-square and Fisher exact tests for statistical significance, with $P < 0.05$ considered significant, were performed using a statistical software package (SPSS Inc., Chicago, IL, USA).

**Results**

A total of 100 microcalcification lesions of 96 patients were eligible for this study. Four patients had bilateral breast microcalcification lesions. No patient was excluded from this study. Their mean age was 49.4 years; median age was 50 years (age range, 28–85 years).

The median interval from MR imaging to mammography was 13 days (range, 0–36 days); the mean interval was 13 days. The median interval from MR imaging to SVAB was 13 days (range, 0–109 days); the mean interval was 18 days.

SVAB analysis

Of 100 initially scheduled SVAB, all 100 were successful. No specimen radiograph lacked microcalcification and there were no problems during the SVAB procedure.

The histologic results of the 100 SVAB are shown in Table 1. Invasive carcinoma was found in only two cases (2%) and DCIS was identified in 31 cases (31%). High-risk lesions, such as ADH or atypical cells, comprised 8% of all lesions and 59% of all lesions were benign.

Stereotactic vacuum-assisted breast biopsy histologic findings and the subsequent surgical excision were compared. In four lesions (13%; 4/31), DCIS were upgraded to infiltrating carcinoma after surgery and one ADH (20%; 1/5) was upgraded to DCIS. No false-positive diagnoses occurred. Therefore, among the 100 lesions in this study, final histologic analysis showed invasive carcinoma in 6 (6%), DCIS in 28 (28%), high-risk lesions in 7 (7%), and benign lesions in 59 (59%) (Table 1). The 57 patients with 59 benign lesions were advised to undergo imaging follow-up according to our institutional management protocol and all 57 (100%) complied. The mean follow-up time was 772 days (range, 161–1,320 days). No false-negative diagnoses occurred because there was no calcification progression at post-SVAB mammographic follow-up and no delayed repeat SVAB was recommended.

**Table 1** Distribution of histologic findings in 100 SVAB

| Histopathological types | No. of SVAB | Total % | No. of final histology | Total % |
|---|---|---|---|---|
| Malignant | | | | |
| Infiltrating carcinoma | 2 | 2 | 6 | 6 |
| DCIS | 31 | 31 | 28 | 28 |
| High risk | | | | |
| ADH | 5 | 5 | 4 | 4 |
| Atypical cell | 3 | 3 | 3 | 3 |
| Benign | | | | |
| ALH | 3 | 3 | 3 | 3 |
| Sclerosing adenosis | 9 | 9 | 9 | 9 |
| Other benign disorder | 47 | 47 | 47 | 47 |
| Total | 100 | 100 | 100 | 100 |

DCIS ductal carcinoma in situ, ADH atypical ductal hyperplasia, ALH atypical lobular hyperplasia

**Table 2** BI-RADS final assessment category for mammographic microcalcification features in 100 lesions

| Features | BI-RADS category | | | |
|---|---|---|---|---|
| | 3 | 4 | 5 | Total |
| Morphology | | | | |
| Punctate | 27 (84) | 5 (16) | – | 32 |
| Amorphous | 27 (79) | 7 (21) | – | 34 |
| Pleomorphic | 1 (5) | 14 (67) | 6 (28) | 21 |
| Linear | – | 1 (8) | 12 (92) | 13 |
| Total | 55 | 27 | 18 | 100 |
| Distribution | | | | |
| Diffuse | – | – | – | – |
| Regional | – | – | – | – |
| Clustered | 34 (63) | 15 (28) | 5 (9) | 54 |
| Segmental | 20 (46.5) | 11 (25.5) | 12 (28) | 43 |
| Linear | 1 (33) | 1 (33) | 1 (33) | 3 |
| Total | 55 | 27 | 18 | 100 |

Numbers in parentheses are percentages of all lesions with that feature classified in the specified final assessment category. Dash (–) indicates none

BI-RADS Breast Imaging Reporting and Data System (5)

## Mammographic findings

Breast Imaging Reporting and Data System final assessment categories in these 100 microcalcification lesions were category 3 in 55 lesions (55%), category 4 in 27 (27%), and category 5 in 18 (18%). A category 5 classification was given to most lesions described as having linear morphology (Table 2). The PPV for the detection of malignancy for category 3 microcalcifications was 7% (4/55). PPV for the detection of malignancy for category 4 microcalcifications was 48% (13/27). PPV for the detection of malignancy for category 5 microcalcifications was 94% (17/18). PPV for the detection of malignancy for categories 4 and 5 microcalcifications was 67% (30/45) compared with the PPV for category 3 (7%; 4/55) ($P < 0.0001$). Negative

predictive value (NPV) for category 3 microcalcifications was 93% (51/55) compared with the combined NPV for categories 4 and 5 of 33% (15/45) ($P < 0.0001$). No malignancy was discovered in clusters of punctate calcifications (Table 3).

The PPV as a function of BI-RADS features for calcification morphology and distribution is shown in Table 3. Features with high PPV showed the segmental or linear distribution of linear morphology (100%, respectively), segmental distribution of pleomorphic morphology (100%), and cluster distribution of linear morphology (80%).

In 43 dense breasts (breast pattern BI-RADS; extremely dense and heterogeneously dense), 12 malignant calcification lesions were detected and 22 malignant calcification lesions were detected in 57 fatty breasts (breast pattern BI-RADS; scattered fibroglandular densities and almost completely fat). In dense breasts, PPV for categories 4 and 5 microcalcifications was 59% (10/17). In fatty breasts, PPV for categories 4 and 5 microcalcifications was 71% (20/28) ($P = 0.292$). In 43 dense breasts, 17 amorphous morphology microcalcifications (40%) were included, and 19 (33%) were included in 57 fatty breasts ($P = 0.522$).

## Dynamic contrast-enhanced MR imaging findings

Dynamic contrast-enhanced MR imaging showed contrast enhancement in the area of concerning microcalcifications in 32 of 34 malignant microcalcifications and no contrast enhancement in the area of concerning microcalcifications in 61 of 67 benign microcalcifications. There were five false-positive cases and two false-negative cases in the MR imaging findings (Table 4). Therefore, PPV was 86% (32/37) and NPV was 97% (61/63). In 27 BI-RADS mammography category 4 microcalcifications, PPV was 80% (12/15). In 18 BI-RADS mammography category 5 microcalcifications, PPV was 100% (17/17).

There was no mass lesion type in this study (Table 5). Among breast MR imaging distribution modifiers, PPV was highest for segmental (100%) and ductal (95%) enhancement (Table 5).

Among breast MR imaging internal enhancement patterns, PPV was highest for clumped (95%) and heterogeneous (92%) enhancement (Table 5).

Among breast MR imaging signal intensity curve patterns, PPV was highest for rapid/fast (100%), plateau (100%), and washout (100%) pattern (Table 5).

Magnetic resonance imaging findings and pathologies of MR imaging false-positive cases are shown in Table 4. Two high-risk lesions are included. One

**Table 3** Frequency of malignancy as a function of microcalcification morphology and distribution

| Microcalcification | BI-RADS-mammography categories | | | | | | |
|---|---|---|---|---|---|---|---|
| | BI-RADS 3 | | BI-RADS 4 | | BI-RADS 5 | | Total |
| Morphology and distribution | Benignity | Malignancy | Benignity | Malignancy | Benignity | Malignancy | |
| Punctate and clustered | 15 (100) | – | – | – | – | – | 15 |
| Punctate and segmental | 11 (73) | – | 4 (27) | – | – | – | 15 |
| Punctate and linear | – | – | – | – | – | – | – |
| Amorphous and clustered | 14 (74) | 4 (21) | 1 (5) | – | – | – | 19 |
| Amorphous and segmental | 9 (60) | – | 2 (13) | 4 (27) | – | – | 15 |
| Amorphous and linear | 1 (50) | – | – | 1 (50) | – | – | 2 |
| Pleomorphic and clustered | 1 (6.5)[a] | – | 7 (46.6) | 7 (46.6) | – | – | 15 |
| Pleomorphic and segmental | – | – | – | 1 (14) | – | 6 (86) | 7 |
| Pleomorphic and linear | – | – | – | – | – | – | – |
| Linear and clustered | – | – | – | – | 1 (20) | 4 (80) | 5 |
| Linear and segmental | – | – | – | – | – | 6 (100) | 6 |
| Linear and linear | – | – | – | – | – | 1 (100) | 1 |
| Total | 51 | 4 | 14 | 13 | 1 | 17 | 100 |

Numbers in parentheses are percentages of all lesions with that feature classified in the specified final assessment category. Dash (–) indicates none

[a] This case is thinly pleomorphic and clustered microcalcification lesion

**Table 4** Comparison of histology and false-positive cases, false-negative cases with MR imaging findings

| | Histology | | MR imaging |
|---|---|---|---|
| | False positive on MR imaging | False negative on MR imaging | Findings |
| Malignant on MR imaging | Benign calcification | – | Focal and homogeneous |
| | Atypical cell | – | Focal and homogeneous |
| | Sclerosing adenosis | – | Ductal and clumped |
| | ADH | – | Focal and heterogeneous |
| | Benign calcification | – | Focus |
| Benign on MR imaging | – | DCIS, comedo | Diffuse |
| | – | IDC | Diffuse |
| Total | 5 | 2 | |

*Note*: ADH = atypical ductal hyperplasia. DCIS = ductal carcinoma in situ. IDC = invasive ductal carcinoma. Dash (–) indicates none

sclerosing adenosis showed ductal clumped enhancement (Fig. 1).

Two malignant microcalcification lesions were interpreted as negative on MR imaging. In these false-negative cases, diffuse enhancement equal to that of the area outside concerning microcalcifications and the contralateral breast (symmetric enhancement) was noted. High-grade DCIS less than 1 mm was missed. In addition, invasive tubular carcinoma of 3 mm × 8 mm was not identified (Fig. 2).

Magnetic resonance imaging findings and histologic grade of DCIS and IDC are shown in Table 6. High-grade DCIS showed ductal clumped enhancement in 11 of 14 cases (79%). All low- and intermediate-grade DCIS showed medium internal enhancement pattern (100%). High-grade DCIS demonstrated rapid/fast enhancement pattern in 2 of 14 (14%). IDC demonstrated a rapid/fast enhancement pattern in one of five (20%). High-grade DCIS demonstrated a washout pattern in 2 of 14 (14%).

In dense breasts, PPV by MR imaging was 92% (11/12). In fatty breasts, PPV by MR imaging was 84% (21/25) ($P = 1$).

Comparison of dynamic contrast-enhanced MR imaging and mammography

Although 55 BI-RADS mammography category 3 microcalcification lesions included four malignancies with clustered amorphous microcalcifications, dynamic contrast-enhanced MR imaging diagnosed three of four malignancies with BI-RADS mammography

**Table 5** Magnetic resonance imaging findings and frequency of malignancy in 37 positive cases

| Findings | No. of cases (%)[a] | No. of cases with malignancy (%)[b] |
|---|---|---|
| Focus/foci | 1(2) | – |
| Mass | – | – |
| Nonmass-distribution modifiers | | |
| Focal area | 11(30) | 8(73) |
| Linear | – | – |
| Ductal | 21(57) | 20(95) |
| Segmental | 4(11) | 4(100) |
| Regional/multiple regional | – | – |
| Diffuse | – | – |
| Nonmass-internal enhancement | | |
| Homogeneous | 4(11) | 1(25) |
| Heterogeneous | 12(32) | 11(92) |
| Clumped | 21(57) | 20(95) |
| Reticular/dendritic | – | – |
| Kinetic curve assessment initial rise | | |
| Slow | – | – |
| Medium | 34(92) | 29(85) |
| Rapid | 3(8) | 3(100) |
| Kinetic curve assessment initial delayed phase | | |
| Persistent | 21(57) | 16(76) |
| Plateau | 14(38) | 14(100) |
| Washout | 2(5) | 2(100) |
| Total | 37 | 32 |

Dash (–) indicates none

[a] Percentage out of the 37 positive cases on MR imaging

[b] Percentage out of all cases with the indicated findings

category 3 as true positive; therefore, the PPV of BI-RADS mammography category 3 added MR imaging was 1.8% (1/55).

In 27 BI-RADS category 4 microcalcifications, the PPV of contrast uptake of MR imaging was 80% (12/15), which was higher than the 48% (13/27) PPV of BI-RADS mammography 4, although not significantly ($P = 0.056$). In 18 BI-RADS category 5 microcalcifications, the PPV of contrast uptake in MR imaging was 100% (17/17), which was not significantly higher than the 94% (17/18) PPV of BI-RADS mammography 5 ($P = 1$).

**Fig. 1** Sclerosing adenosis in the upper inner quadrant of the left ▶ breast of a 55-year-old woman. **(a)** and **(b)** Left mediolateral oblique view and spot compression magnification mammogram demonstrate mainly punctate microcalcifications in segmental distribution (*arrows*) and a few pleomorphic and clustered microcalcifications (*arrowhead*). On these mammograms, such a microcalcification lesion was classified as BI-RADS category 4. **(c)** Sagittal contrast-enhanced T1-weighted fat-suppressed MR imaging of the left breast reveals clumped ductal enhancement in the upper inner quadrant (*arrow*). Note also the vascular enhancement under the clumped ductal enhancement (*arrowheads*)

The PPV of contrast uptake in MR imaging was 86% (32/37), which was significantly higher than the 67% (30/45) PPV of BI-RADS mammography 4 and 5
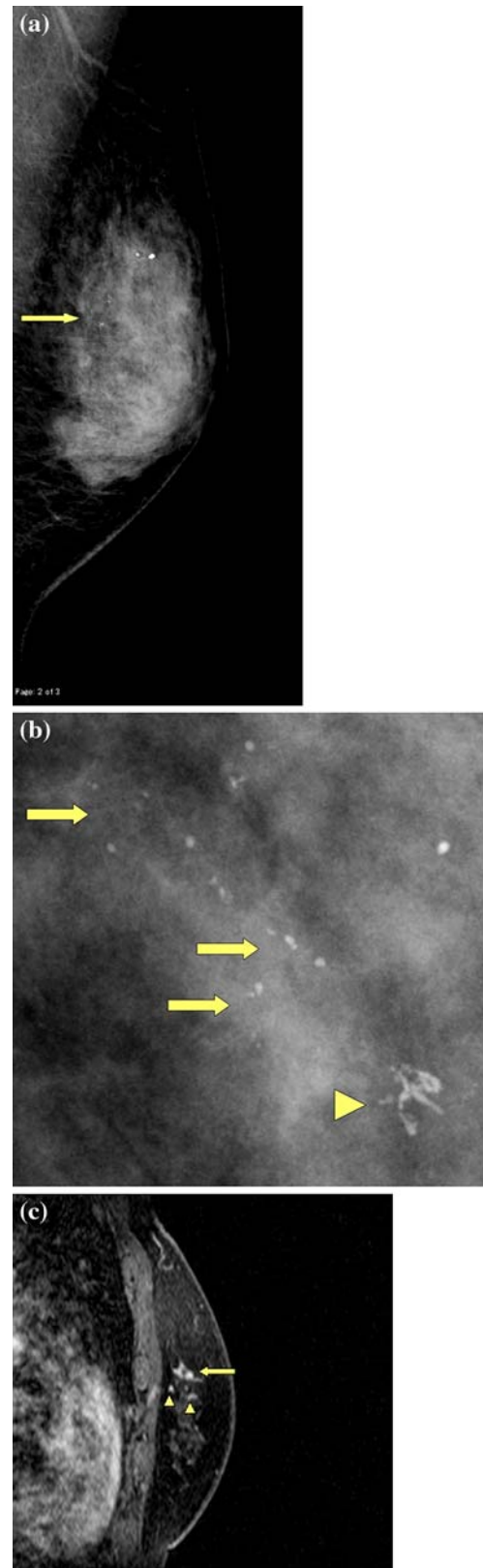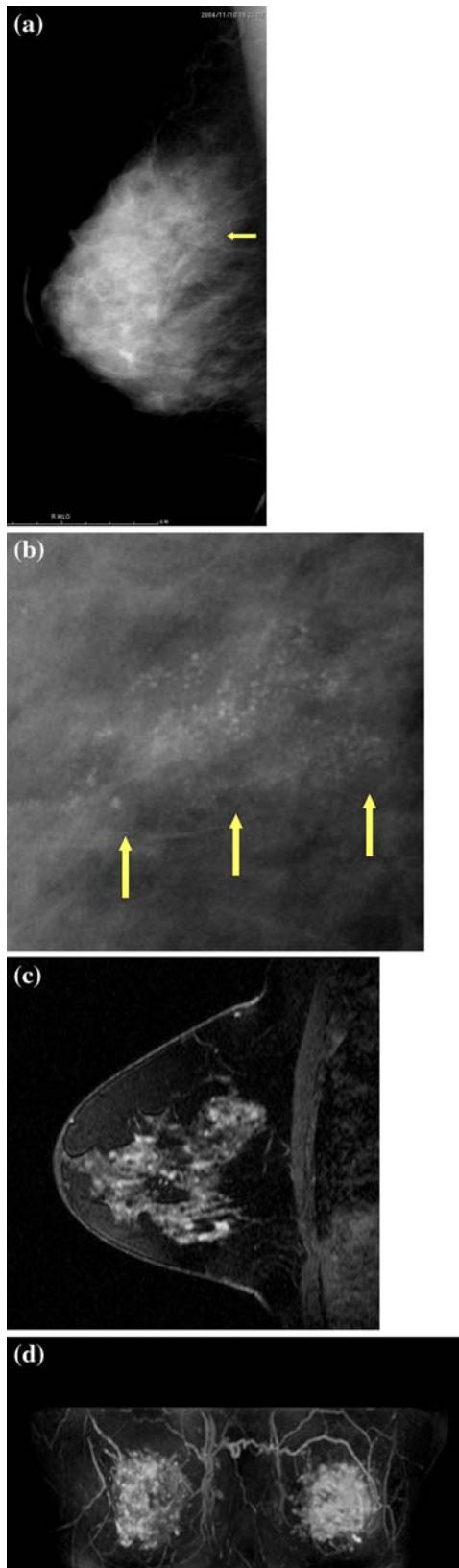
◀**Fig. 2** Invasive tubular carcinoma of 3 mm × 8 mm in the upper outer quadrant of the right breast of a 50-year-old woman. **(a)** and **(b)** Right mediolateral oblique view and spot compression magnification mammogram demonstrate amorphous and segmental microcalcifications (*arrows*) classified as BI-RADS category 4. **(c)** Sagittal contrast-enhanced T1-weighted fat-suppressed MR imaging of the right breast shows diffuse stippled parenchymal enhancement in the upper outer quadrant. **(d)** Maximum intensity projections image shows bilateral diffuse stippled parenchymal enhancement in the bilateral breasts

In dense breasts, the PPV of contrast uptake in MR imaging was 92% (11/12), which was higher than the 59% (10/17) PPV of BI-RADS mammography 4 and 5, although not significantly ($P = 0.06$). In fatty breasts, the PPV of contrast uptake in MR imaging was 84% (21/25), which was not higher than the 71% (20/28) PPV of BI-RADS mammography 4 and 5 ($P = 0.224$).

## Discussion

### BI-RADS category 3 microcalcifications

The rate of malignancy for BI-RADS category 3 microcalcifications is not well established because many such lesions are followed up. Very little information on the result of SAVB is available for BI-RADS category 3 microcalcifications. Mendez et al. [11] reported a 7% (6 of 90) incidence breast carcinoma (infiltrating carcinoma and DCIS) in BI-RADS category 3 microcalcifications by SVAB. In our series, 4 (7%) of 55 BI-RADS category 3 microcalcifications were malignant as a consequence of SVAB. The recommended percentage among BI-RADS 3 lesions is 2% or fewer [12, 13]. These criteria are used by most mammographers in the United States and throughout the world; however, 2% or fewer are based on follow-up mammograms [12, 13] and not on a biopsy series. Therefore, about 7% of BI-RADS category 3 microcalcifications may be malignant among consecutive SVAB cases. However, the malignancy rate of BI-RADS category 3 microcalcifications is relevant to the criteria of BI-RADS category 3 microcalcifications. Sickles defined probably benign microcalcifications using strict criteria such as clustered microcalcifications that were round or oval on magnification mammograms [12]. However, BI-RADS states that most approaches to category 3 probably benign lesions are intuitive [5] and there is no standardized and universally accepted criteria for probably benign microcalcifications. In our study, a category 3 classification was given to microcalcification

($P = 0.033$). NPV of BI-RADS mammography 3 was 93% (51/55) versus the 97% (61/63) NPV of MR imaging ($P = 0.167$).

**Table 6** Magnetic resonance imaging findings and histologic grade

| Findings | Low-grade DCIS (%) | Intermediate-grade DCIS (%) | High-grade DCIS (%) | IDC (%) | Total |
|---|---|---|---|---|---|
| Nonmass-distribution modifiers | | | | | |
| Focal area | 2(29) | 3(50) | 1(7) | 2(4) | 8 |
| Ductal | 4(57) | 3(50) | 11(79) | 2(40) | 20 |
| Segmental | 1(14) | – | 2(14) | 1(20) | 4 |
| Nonmass-internal enhancement | | | | | |
| Homogeneous | – | – | 1(7) | – | 1 |
| Heterogeneous | 3(43) | 3(50) | 2(14) | 3(60) | 11 |
| Clumped | 4(57) | 3(50) | 11(79) | 2(40) | 20 |
| Kinetic curve assessment initial rise | | | | | |
| Medium | 7(100) | 6(100) | 12(86) | 4(80) | 29 |
| Rapid | – | – | 2(14) | 1(20) | 3 |
| Kinetic curve assessment initial delayed phase | | | | | |
| Persistent | 3(43) | 5(83) | 8(57) | – | 16 |
| Plateau | 4(57) | 1(17) | 4(29) | 5(100) | 14 |
| Washout | – | – | 2(14) | – | 2 |
| Total | 7 | 6 | 14 | 5 | 32 |

Percentage out of the subtype histologic grade lesions with the classified findings. Dash (–) indicates none

lesions described as having 15 cluster punctate, 11 segmental punctate, 14 cluster amorphous, 9 segmental amorphous, 1 linear amorphous, and 1 thinly cluster pleomorphic microcalcifications (Table 3). Among 55 category 3 microcalcifications, only 4 cluster amorphous microcalcification lesions were revealed as malignant and the remainder were benign. The findings of this study underline that there are many category 3 classified microcalcifications besides Sickles' strict criteria such as cluster punctate microcalcifications. In addition, in the four malignant clustered amorphous microcalcifications assigned as BI-RADS mammography category 3, dynamic contrast-enhanced MR imaging diagnosed three of the four malignancies with clustered amorphous microcalcifications as true positive. Therefore, the PPV of BI-RADS mammography category 3 microcalcifications with MR imaging was 1.8% (1/55). These data showed that dynamic contrast-enhanced breast MR imaging is able to differentiate malignant microcalcifications from BI-RADS mammography category 3 microcalcifications. Four studies suggested dynamic contrast-enhanced breast MR imaging was not reliable in the differentiation of benign from malignant microcalcifications [19–22], whereas one recent report indicated that dynamic contrast-enhanced MR imaging is able to differentiate benign from malignant disease associated with microcalcification with considerably greater accuracy than mammography or ultrasound [18]. This difference may come from the different population of these studies or the variation of magnetic field strength, breast coil specifications, pulse sequences, and other parameters. Therefore,

dynamic contrast-enhanced breast MR imaging has not yet found a role in the clinical evaluation of screening that detected microcalcification lesions of the breast. However, our study suggested that dynamic contrast-enhanced breast MR imaging may be an accurate imaging modality for assessing BI-RADS category 3 microcalcifications.

BI-RADS categories 4 and 5 microcalcifications

In this study, PPVs in the result of SAVB were 48% for BI-RADS category 4 microcalcifications and 94% for category 5 microcalcifications. These results are superior to those previously reported by Mendez et al. [11]. In their study of 947 lesions that underwent SVAB, malignancy (included atypia) was present in 16% of 621 BI-RADS category 4 microcalcifications compared with 83% BI-RADS category 5 microcalcifications. Moreover, another study reported that malignancy (including ADH) was present in 20% of 2,439 BI-RADS category 4 lesions compared with 85% BI-RADS category 5 lesions in a study of 2,874 lesions including 2,013 (70%) microcalcification lesions that performed SVAB [10]. Subsequently, two published studies reported that PPVs ranged from 30 to 34% for BI-RADS category 4 lesions (not only microcalcification lesions) versus 81–97% for BI-RADS category 5 lesions (not only microcalcification lesions) [8, 9]. These differences may come from the different populations of these studies or inconsistent criteria for the BI-RADS category. In this study, the PPV of BI-RADS mammography category 4 microcalcifications with MR imaging was 80% (12/15) with three

false-positive lesions (one ADH, one Atypia, and one sclerosing adenosis) and one false negative (3 mm × 8 mm tubular invasive carcinoma). Although not significantly ($P = 0.056$), the PPV of contrast uptake in MR imaging was 80% (12/15), higher than the 48% (13/27) PPV of BI-RADS mammography 4. These data suggested that dynamic contrast-enhanced breast MR imaging was able to reduce the number of SVAB that produced benign results. However, as far as BI-RADS mammography category 5 is concerned, dynamic contrast-enhanced breast MR imaging does not contribute to the full diagnostic mammography workup because the PPV of BI-RADS mammography 5 was 94% (17/18), which was not significantly lower than the 100% (17/17) PPV of contrast uptake in MR imaging in 18 BI-RADS category 5 microcalcifications ($P = 1$) in our study.

### BI-RADS mammography features of calcifications morphology and distribution

In calcification morphology, all 30 punctate morphology microcalcifications, regardless of distribution (including 15 segmental, not including linear), were benign (100%) in this study. Mammographically, punctate microcalcifications, regardless of distribution, may be considered probably benign, especially when using Sickles' strict criteria such as cluster punctate microcalcifications, although D'Orsi commented that punctate calcifications in segmental or linear distribution would be at least suspicious [26]. In this study, 25% (9/36) amorphous morphology microcalcifications were malignant. The rate of malignancy for amorphous microcalcifications is compatible with that reported by Berg et al. [27]. They suggested that amorphous calcifications should be considered suspicious and referred for biopsy because 20% amorphous calcifications were malignant in 150 biopsied amorphous microcalcifications. We agree with them overall, but 75% (27/36) amorphous morphology microcalcifications were benign in this study and 80% in Berg's study. In this study, dynamic contrast-enhanced MR imaging diagnosed three of four malignancies with clustered amorphous microcalcifications as true positive, although four malignant clustered amorphous microcalcifications were assigned as BI-RADS mammography category 3. Therefore, we recommend breast MR imaging as a good predictable modality for differential diagnosis for amorphous microcalcifications to minimize unnecessary SVAB. In this study, 64% (14/22) pleomorphic morphology microcalcifications and 92% (11/12) linear morphology microcalcifications were

malignant. For calcification distribution, 28% (15/54) clustered distribution microcalcifications, 40% (17/43) segmental distribution microcalcifications, and 67% (2/3) linear distribution microcalcifications were malignant in this study. Moreover, the features with a high PPV were segmental or linear distribution of linear morphology (100%, respectively), segmental distribution of pleomorphic morphology (100%), and cluster distribution of linear morphology (80%). These data suggest that assigning final assessment BI-RADS categories with a combination of microcalcification morphology and distribution may improve standardization in mammographic interpretation.

### BI-RADS-MR imaging features

The frequency of malignancy was highest in segmental enhancement (100% malignancy) and ductal clumped enhancement (95% malignancy). Previous studies have reported PPVs of 31–86% for segmental or linear and ductal enhancement [28–30]. Although Liberman et al. suggested that the frequency of cancer may be lower among lesions showing ductal enhancement at MR imaging than among lesions evident as ductal distribution of calcification on mammography or ductal extension on sonography [31], the PPV of 95% for ductal clumped enhancement was high in this study. This may result from the different population in these studies or interobserver variability in breast MR imaging interpretation. We note that one sclerosing adenosis showed ductal clumped enhancement in this study.

For kinetic features, the washout kinetic pattern was only 6% (2/32) of malignancy in this study, reflecting the high proportion of DCIS (88%; 28/32). In addition, two washout kinetic pattern malignancies were high-grade DCIS, however, washout kinetic pattern high-grade DCIS was present in only 14% of 14 high-grade DCIS. Moreover, a rapid/fast kinetic pattern was also only 9% (3/32) of malignancy (one invasive ductal carcinoma and two high-grade DCIS) in this study. This result suggests few DCIS with a washout kinetic pattern and/or rapid/fast kinetic pattern. Liberman et al. suggested that reliance on the presence of washout to diagnose cancer may impair the ability to detect DCIS [28]. Therefore, the ability of dynamic contrast-enhanced breast MR imaging in patients with mammographically detected microcalcifications with the criterion of signal intensity curves is potentially impaired because it is necessary for mammographically detected microcalcifications to include many DCIS. Hence, three negative studies with the criterion of

signal intensity curves suggest that dynamic contrast-enhanced breast MR imaging was not reliable in the differentiation of benign from malignant microcalcifications [19, 20, 22]. The other negative studies used 0.5T MR imaging that was not state-of-art for breast MR imaging [21].

In this study, two malignant microcalcification lesions (high-grade DCIS less than 1 mm and invasive tubular carcinoma of 3 mm × 8 mm) were interpreted as negative on MR imaging. In these false-negative cases, diffuse enhancement equal to that of the area outside concerning microcalcifications and the contralateral breast (symmetric enhancement) was noted. Liberman et al. suggest that diffuse enhancement lowers the sensitivity of breast MR imaging [32]. In premenopausal women, performing breast MR imaging within the second week of the menstrual cycle may improve the sensitivity and specificity of dynamic contrast-enhanced breast MR imaging because diffuse enhancement such as unidentified breast objects confounding MR imaging interpretation are reduced [32, 33].

### Breast density

In dense breasts, the PPV of contrast uptake in MR imaging was 92% (11/12), which was higher than the 59% (10/17) PPV of BI-RADS mammography 4 and 5, although not significantly ($P = 0.06$), while in fatty breasts, it was 84% (21/25) compared with the 71% (20/28) PPV of BI-RADS mammography 4 and 5 ($P = 0.224$). There was no significance ($P = 0.522$) concerning the proportion of amorphous microcalcification cases between dense and fatty breast cases, although we think that the proportion of amorphous microcalcification cases may have influenced the PPVs of mammography in dense breasts or fatty breasts. These data suggest that breast MR imaging is superior to mammography in dense breasts in the evaluation of screening that detected microcalcifications, although we know that breast MR imaging can offer advantages over conventional imaging methods in dense breasts in general, not only limited to microcalcifications [34].

### Management protocol for microcalcifications

We propose the following management protocol for concerning microcalcifications from the results in this study.

Punctate microcalcifications must show a probably benign finding, should be assigned as BI-RADS category 3 and undergo short-interval follow-up. It is not necessary for punctate microcalcifications to undergo SVAB and breast MR imaging.

Amorphous microcalcifications should be considered suspicious and referred for SVAB. However, we recommend that breast MR imaging should be used as a good predictable modality for the differential diagnosis of amorphous microcalcifications to minimize unnecessary SVAB. We also recommend that amorphous microcalcifications with positive MR imaging should undergo SVAB, whereas negative cases, that do not want to undergo SVAB, may receive short-interval follow-up.

Pleomorphic morphology microcalcifications have a moderate PPV; however, they should be considered suspicious and assigned as BI-RADS category 4. Therefore, we recommend that pleomorphic microcalcifications with positive MR imaging should undergo SVAB, whereas negative cases, that do not want to undergo SVAB, may receive short-interval follow-up.

Breast Imaging Reporting and Data System mammography category 5 microcalcification lesions such as linear microcalcifications should undergo SVAB without breast MR imaging.

### Limitation

This study has several limitations. The study population was small, and the study was limited by a moderate follow-up time for benign lesions diagnosed by SVAB (mean follow-up time; 772 days). Although our experience with dynamic contrast-enhanced breast MR imaging for screening detected microcalcification lesions is limited, we think the results with our data are very promising. A larger study population and more outcome data are needed to confirm our results. Finally, MR imaging studies were diagnosed prospectively by two radiologists with consensus, but there may be inter- and intraobserver variability in breast MR imaging interpretation. Continued development of methods to improve standardization in breast MR imaging interpretation is needed.

We do not analyze the cost of breast MR imaging. Although breast MR imaging with imperfect PPV and NPV may not prove to be a cost-effective modality to help differentiate benign from malignant lesions, cost-effectiveness studies that consider not only objective costs but also subjective costs like patient preferences are needed to determine whether follow-up based on benign findings at MR imaging is optimal in comparison with proceeding to SVAB. Moreover, follow-up mammography may be associated with reduced morbidity when compared to SVAB. Further studies concerning cost-effective analyses to directly compare breast MR imaging and SVAB are needed.

## Conclusion

In the evaluation of screening detected microcalcification lesions, dynamic contrast-enhanced breast MR imaging provides additional information with high PPV and NPV, and may therefore offer an alternative to SVAB for women who do not want to undergo SVAB with equivocal findings following full mammographic assessment. Dynamic contrast-enhanced breast MR imaging can demonstrate malignant microcalcifications detected by screening mammography and can be recommended in the evaluation of equivocal microcalcifications prior to SVAB. However, breast MR imaging with imperfect PPV and NPV cannot replace SVAB.

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