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Management for BI-RADS category 3 lesions detected in preoperative breast MR imaging of breast cancer patients

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Abstract

Objective To retrospectively evaluate characteristics of and determine appropriate follow-up recommendations for BI-RADS category 3 lesions detected in preoperative MRI of breast cancer patients.

Methods BI-RADS category 3 assessments were identified from the breast MRI database for 5,110 consecutive breast cancer patients who had undergone preoperative MRI and surgery. Patient and lesion characteristics, malignancy rate, and interval between lesion detection and cancer diagnosis were analysed. Histopathological results or imaging at or after 2-year follow-up were used as reference standards.

Results Of the 626 lesions, morphological features included a single focus in 26.5% (n = 166), multiple foci in 47.1% (n = 295), mass in 21.7% (n = 136) and non-mass enhancement in 4.6% (n = 29). Cancer was found in 0.8% (5/626) at a median interval of 50 months (range, 29–66 months). Malignancy rate according to morphological feature was: 1.8% (3/166) in a single focus, 0.7% (1/136) in mass and 3.4% (1/29) in non-mass enhancement. All detected cancers were stage 0 or IA.

Conclusions Annual follow-up might be adequate for BI-RADS category 3 lesions detected at preoperative MRI because of the 0.8% (5/626) malignancy rate, long interval between lesion detection and cancer diagnosis, and early stage of diagnosed cancers.

Key Points
• *BI-RADS category 3 lesions on preoperative MRI had 0.8% malignancy rate.*
• *All cancer diagnoses from BI-RADS 3 occurred after 24-month follow-up.*
• *Annual follow-up might be adequate for BI-RADS 3 detected on preoperative MRI.*

Keywords Breast cancer · Magnetic resonance imaging · Follow-up studies · Imaging · Appointments and schedule

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Introduction

It has been well established that Breast Imaging Reporting and Data System (BI-RADS) final assessment category 3 lesions, having malignancy rates of less than 2% for mammography, should be managed with short-term imaging follow-up (typically at 6, 12 and 24 months) rather than biopsy [1, 2]. Short-term follow-up is advantageous because it avoids the risks and costs of invasive tissue sampling for the majority of benign lesions. In addition, the few malignancies detected at follow-up imaging have been small and at an early stage [1–6].

In the field of breast magnetic resonance (MR) image interpretation, previous studies have used various criteria for BI-RADS category 3 assessments in different populations, with the reported incidence of BI-RADS category 3 assignment ranging from 6% to 8.5% and their malignancy rate ranging

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from 0.9% to 4.3% [7–10]; these results are comparable with those from mammography. Similar to mammography screening, short-term follow-up (at 6, 12 and 24 months) has been recommended for category 3 lesions detected at MR imaging; however, there has been a lack of evidence regarding short-term follow-up for BI-RADS category 3 lesions detected at MR imaging [11]. Considering the high cost, high false-positive rate and intolerability of MR examinations, appropriate management recommendations should be further investigated. Previous studies have shown that 10.9% of patients undergoing preoperative MR imaging after the diagnosis of breast cancer have coincidental lesions with BI-RADS category 3 [12]. Unlike women undergoing screening MR imaging, women receiving preoperative MR imaging subsequently undergo surgery, chemotherapy or radiation therapy, which may lead to decreased screening sensitivity as well as decreased tumour growth. Therefore, the purpose of our study was to retrospectively evaluate characteristics of and determine appropriate follow-up recommendations for BI-RADS category 3 lesions detected at preoperative MR imaging of patients with newly diagnosed breast cancers.

Materials and methods

Subject population

Our Institutional Review Board approved this retrospective analysis, and informed consent was waived. Between January 2007 and December 2012, prospectively recorded BI-RADS category 3 assessments were identified from the breast MR imaging database. Of the 5,110 consecutive women who had undergone preoperative MR examinations and curative surgery for breast cancer, 683 (13.4%) women had BI-RADS category 3 lesions. Among them, 57 women were excluded due to unavailability of 2-year follow-up data (n = 45) or total mastectomy including BI-RADS category 3 lesions (n = 12). We excluded cases with total mastectomy as their reference standard was not available. Histopathological mapping or surgical excision after localization was not routinely performed for BI-RADS category 3 lesions. Finally, 626 BI-RADS category 3 lesions in 626 women (median age, 47 years; range, 23–81 years) comprised our study population (Table 1). Of the 626 women, 7.8% (49/626) had familial history of breast cancer (n = 43) or were BRCA mutation carriers (n = 6).

MR imaging evaluation

All MR examinations were performed using a 1.5-T MR imager (Signa; GE Medical System, Milwaukee, WI, USA) with a dedicated eight-channel bilateral breast coil (GE Medical System). Sagittal fat-suppressed T2-weighted fast spin-echo MR imaging was performed using the following image parameters: repetition time msec/echo time msec, 5,500–7,150/

Table 1 Clinicopathological characteristics of 626 women with BI-RADS category 3 lesions on preoperative MR imaging

Characteristics	Women with subsequently diagnosed cancer (n = 5)	Women without cancer (n = 621)
Age (y)		
Mean ± standard deviation	51.0 ± 10.9	47.5 ± 8.3
Age category		
< 50 years	3 (0.7)	454 (99.3)
≥ 50 years	2 (1.2)	167 (98.8)
Risk factor		
Mutation in *BRCA1* or *BRCA2*	0 (0)	6 (100)
Familial history of breast cancer	0 (0)	43 (100)
Stage of index cancer		
Ductal carcinoma in situ	1 (1.3)	77 (98.7)
Invasive, stage I	2 (0.7)	270 (99.3)
Invasive, stage II	2 (0.9)	228 (99.1)
Invasive, stage III	0 (0)	46 (100)
Histological type of index cancer		
Ductal cancer	5 (0.8)	603 (99.2)
Lobular caner	0 (0)	18 (100)
Subtype of index cancer		
Luminal A-like	3 (0.7)	427 (99.3)
Luminal B-like	1 (1.9)	52 (98.1)
Triple negative	1 (1.1)	90 (98.9)
Her2 positive	0 (0)	52 (100)

Numbers in parentheses are percentage

HER2 human epidermal growth factor receptor 2

85.2; matrix, 256 × 160; field of view, 200 × 200 mm; section thickness, 1.5 mm; no gap. Dynamic contrast-enhanced MR examinations included one pre-contrast and five post-contrast bilateral sagittal image acquisitions using a fat-suppressed T1-weighted three-dimensional fast spoiled gradient-echo sequence with parallel imaging (6.5/2.5; matrix, 256 × 160; flip angle, 10°; field of view, 200 × 200 mm; section thickness, 1.5 mm; no gap). The acquisition time of each post-contrast series was 76 s. Five post-contrast image series were obtained at 91, 180, 360, 449 and 598 s after the start of contrast administration. A dose of 0.1 mmol/kg gadobutrol (Gadovist, Bayer Healthcare, Berlin, Germany) was injected into an antecubital vein using an automated injector (Spectris Solaris; Medrad Europe, Maastricht, The Netherlands) at a rate of 2 ml/s, followed by a 20-ml saline flush.

MR imaging interpretation

MR imaging was prospectively interpreted by one of five radiologists with 7–15 years of experience in breast MR interpretation and intervention according to the fourth edition of BI-RADS lexicon on a Picture Archiving and Communication System (PACS) [11]. The following characteristics indicated a BI-RADS category 3 assessment: (1) an oval or round mass with circumscribed margin and without suspicious kinetics; (2) focal or regional non-mass enhancements (NME) with internal homogeneous or stippled pattern; (3) isolated and

dominant focus without suspicious kinetics; and (4) multiple bilateral foci, including prominent foci. Multiple bilateral and diffusely distributed foci represented background parenchymal enhancement and were considered BI-RADS category 2 [13]. However, multiple bilateral foci with some asymmetrical distribution or lesions including several prominent foci were considered BI-RADS category 3. Kinetic features were assessed by drawing a region of interest over the most suspicious portion of the lesion to measure the signal intensity change through dynamic images on a PACS. High-resolution PACS monitors were used for interpretation in conjunction with patients' clinical history and other breast imaging examinations including mammography or ultrasound (US). One day before surgery, all patients routinely underwent preoperative mammography and US in addition to MR examinations. The BI-RADS final assessment category was determined and recorded based on MR images in conjunction with mammography and US findings [11].

To evaluate interobserver variability of MR image interpretations, three fellowship-trained breast radiologists independently reanalysed MR images according to the BI-RADS Atlas [11] without knowledge of the original MR image interpretations and histopathological information.

Follow-up protocol

For BI-RADS category 3 lesions detected at preoperative MR imaging, 6-, 12- and 24-month follow-up MR imaging was recommended. When the lesion was determined have a correlative mammography or US finding, follow-up was performed with mammography or US. If the lesion was stable for 24 months, it was downgraded to BI-RADS category 2. Annual mammography with US was performed thereafter. If the BI-RAS category 3 lesion exhibited increase in size or change in shape during follow-up, a biopsy was performed.

Data and statistical analysis

The patient and lesion characteristics, all available images, histopathology results, and the interval between lesion detection and cancer diagnosis were reviewed. Rate of malignancy from BI-RADS category 3 lesions was calculated. Independent sample t tests or Fisher's exact tests were used to compare characteristics between women with subsequently breast cancer diagnosis and women without cancer.

In addition, hypothetical changes in the frequency and malignancy rate of BI-RADS category 3 lesions were calculated to identify an adequate definition of BI-RADS category 3 assessment to reduce false-positive findings and to achieve malignancy rate less than 2%.

Interobserver variability for interpretation of MR images of three radiologists was evaluated by calculating the Fleiss kappa (k) coefficient. A kappa statistic of 0.2 or less was

considered slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–0.99, almost perfect agreement [14]. All statistical analyses were performed using statistical software (SPSS, version 20.0; SPSS, Chicago, IL, USA). A P value of less than .05 was considered a significant difference.

Results

Of the 626 BI-RADS category 3 lesions, 166 (26.5%) had a single focus, 295 (47.1%) had multiple foci, 136 (21.7%) had masses, and 29 (4.6%) had NME on initial MR images (Table 2). A case of bilateral multiple foci was counted as one lesion. During follow-up, percutaneous biopsy or surgical excision was performed for 37 (5.9%) lesions due to interval change. Among them, 32 (86.5%) were benign and 5 (13.5%) were cancers.

With regard to the characteristics of malignant cases, 80% (4 of 5) were invasive ductal carcinoma (median tumour size, 0.6 cm; range, 0.1-1.0 cm) and 20% (1 of 5) were ductal carcinoma in situ (Table 3). Eighty% of them (4/5) were found in the contralateral breast and 20% were in the ipsilateral breast (Table 3). Three cancers presented as increased masses at follow-up US. The other two cancers presented as increased microcalcifications at follow-

Table 2 MR imaging features of 626 BI-RADS category 3 lesions on preoperative MR imaging

	Malignancy (n = 5)	Benign (n = 621)	P-value
Background parenchymal enhancement			0.529
Minimal	1 (0.5)	183 (99.5)	
Mild	1 (0.6)	168 (99.4)	
Moderate	1 (0.6)	173 (99.4)	
Marked	2 (2.0)	97 (98.0)	
Laterality to the index cancer			0.179
Ipsilateral	1 (1.0)	103 (99.0)	
Contralateral	4 (1.4)	274 (98.6)	
Bilateral	0 (0)	244 (100)	
Morphological features			0.069
Single focus	3 (1.8)	163 (98.2)	
Multiple foci	0 (0)	295 (100)	
Mass	1 (0.7)	135 (99.3)	
Shape			NA
Oval/lobular	0	95 (100)	
Round	0	16 (100)	
Irregular	1 (4)	24 (96)	
Margin			NA
Circumscribed	0 (0)	99 (100)	
Irregular	1 (2.7)	36 (97.3)	
Non-mass enhancement	1 (3.4)	28 (96.6)	
Distribution			NA
Focal	1 (4.5)	21 (95.5)	
Linear	0 (0)	5 (100)	
Segmental	0 (0)	1 (100)	
Regional	0 (0)	1 (100)	

Numbers in parentheses are percentage

NME non-mass enhancement, *NA* not applicable

Table 3 Characteristics of BI-RADS category 3 lesions subsequently diagnosed with cancer

Patient age	Interval[a] (months)	Site[b]	Imaging finding	Pathological type	Size (cm)	Nodal status	Hormonal status
41	66	Contralateral	Focus	IDC	0.5	Negative	ER (−), PR (−), HER2 (−)
59	40	Contralateral	NME	DCIS	4.1	Negative	ER (−), PR (−), HER2 (−)
66	54	Contralateral	Focus	IDC	0.7	Negative	ER (+), PR (+), HER2 (−)
45	29	Contralateral	Focus	IDC	1.0	Negative	ER (+), PR (−), HER2 (−)
44	61	Ipsilateral	Mass	IDC	0.1	Negative	ER (−), PR (−), HER2 (+)

[a] Interval between preoperative MR imaging and breast cancer diagnosis

[b] BI-RADS category 3 cancer site compared with initial breast cancer

BI-RADS breast imaging reporting and data system, *IDC* invasive ductal carcinoma, *DCIS* ductal carcinoma in situ, *ER* oestrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

up mammography. No cancer was found at follow-ups prior to 24 months after initial MR images. Two cancers were diagnosed at a 25 month to 48 month follow-up interval. The other three cancers were diagnosed at a 49 month to 72 month follow-up interval. Thus, the malignancy rate was 0.8% (5 of 626).

The cancers originally presented on preoperative MR images as a focus in 3 cases (Fig. 1), a mass in one case and a NME in one case (Table 2). No cancer was found in the remaining 589 lesions at a median of 53 months (mean 53 months; range 25-82 months) imaging follow-up; of the 589 lesions, 148 disappeared and 441 decreased or showed stability (Fig. 2). When the finding of multiple foci (Fig. 3) was reclassified as category 2 assessment, the frequency of BI-RADS category 3 assessment changed from 13.4% (683 of 5110) to 7.6% (388 of 5110) and malignancy rate changed from 0.8% (5 of 626) to 1.5% (5 of 331).

The overall agreement for interpretation of lesion morphologic features was substantial (k = 0.63). Substantial agreement for mass shape (k = 0.61), mass margin (k = 0.78), and almost perfect agreement for distribution of NME was (k = 0.89) found.

Discussion

Our results showed that the malignancy rate of BI-RADS category 3 lesions detected at preoperative breast MR imaging was 0.8% (5/621), and cancers were detected at a median of 50 months (range, 29–66 months) imaging follow-up.

Our study's 0.8% malignancy rate of BI-RADS category 3 lesions is in accordance with the less than 2% malignancy rate suggested for BI-RADS category 3 assessment in the field of screening mammography [1–4, 15]. However, our result is lower than that in previous studies using MR images, in which the malignancy rates ranged from 0.9–4.3% [7–11]. Grimm et al. reported a 4.3% malignancy rate in a study including 57.5% high–risk screening [9]. Spick et al. reported a 0.9% malignancy rate in a study including patients who were not at high risk for breast cancer and had no personal history of breast cancer [8], which is closer to our result. Another recent study reported that the malignancy rate of BI-RADS category 3 lesions was greater in women with a personal breast cancer history or germline mutation than women without such risk factors (3.8% vs. 0%) [10]. In that study, no malignancy was found in the 27 preoperative MR examinations to evaluate disease extent [10]. Based on our results and those of previous studies, the malignancy rate for BI-RADS category 3 lesions is higher for high-risk screening than in the preoperative MRI setting for newly diagnosed cancer patients.

Although the BI-RADS Atlas has not suggested different management recommendations based on the indications of breast MR examinations, women with BI-
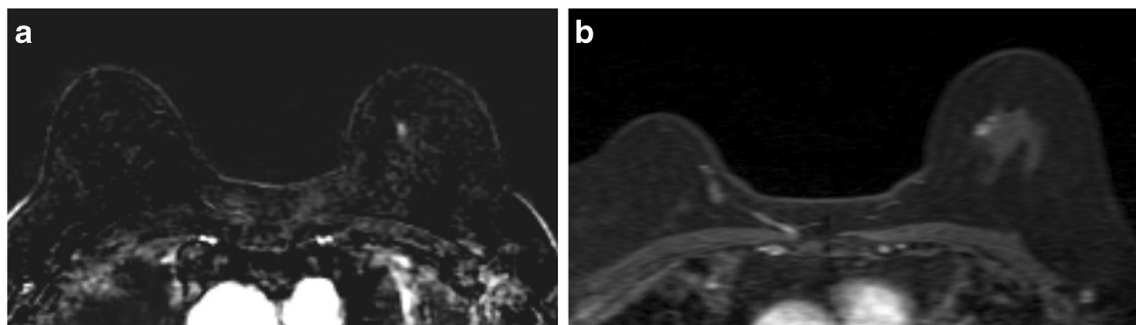
Fig. 1 Post-contrast-enhanced axial MR images in a 66-year-old woman who underwent breast-conserving surgery for invasive breast cancer in the right breast. This case indicates a malignant case arising from BI-RADS category 3 lesion. (*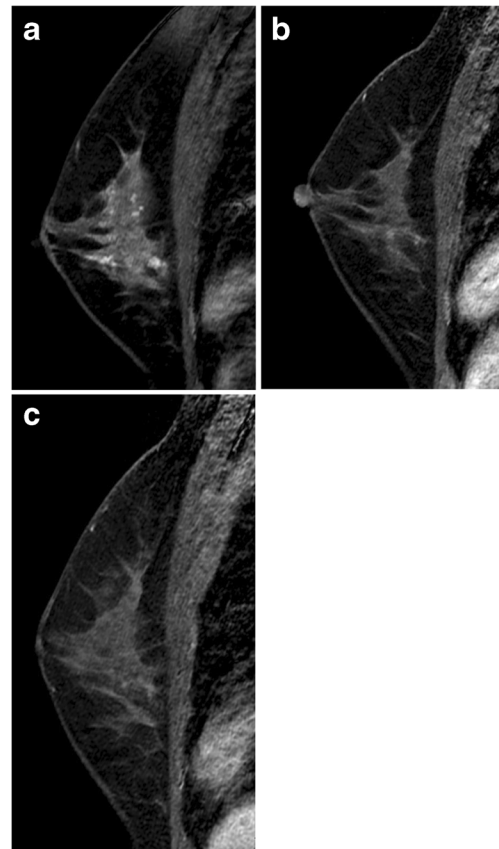*a**) Preoperative breast MR image demonstrates a focus in the left breast that was assessed to be a BI-RADS category 3. (**b**) At 54-month-follow-up, the focus appears larger. Core needle biopsy and surgical histopathology revealed a 0.7-cm invasive ductal carcinoma
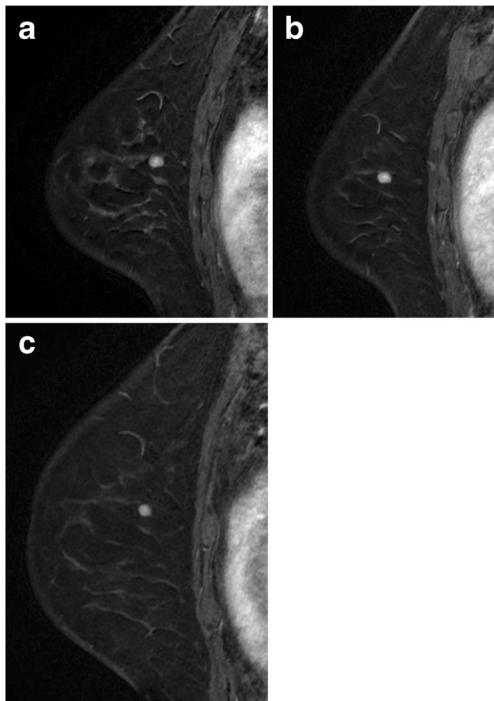
Fig. 2 Post-contrast-enhanced sagittal MR images in a 46-year-old woman who underwent breast conserving surgery, radiation therapy and adjuvant chemotherapy with tamoxifen for invasive breast cancer in the left breast. This case indicates a decreased size of the case initially classified as BI-RADS category 3. (**a**) Preoperative breast MR image demonstrates an 8-mm enhancing mass in the left breast that was assessed to be BI-RADS category 3. (**b**) At 12-month-follow-up MR examination, the mass had decreased to 7 mm. (**c**) At 42-month-follow-up MRI, the mass had further decreased to 5 mm

Fig. 3 Post-contrast-enhanced sagittal MR images in a 48-year-old woman who underwent breast-conserving surgery, radiation therapy and adjuvant chemotherapy for invasive breast cancer in the right breast. This case indicates a disappeared case initially classified as BI-RADS category 3. (**a**) Preoperative breast MR image of right breast demonstrates multiple foci with prominent foci in the left breast that was assessed to be BI-RADS category 3. (**b**) At 7-month-follow-up MRI, the multiple foci disappeared. (**c**) At 45-month-follow-up MRI, no cancer was found

RADS category 3 lesions on MR images have heterogeneous risk for the occurrence of another breast cancer; thus, consideration of tailored follow-up recommendations might be warranted. In our study, five cancers arising from BI-RADS category 3 lesions were detected during a long interval period (median, 50 months, range, 29–66 months) between initial detection and cancer diagnosis. Notably, no cancer was found at less than 24 months follow-up. However, previous studies including high-risk populations have reported that the majority of cancers from BI-RADS category 3 lesions were detected during a 24-month follow-up period [7–10, 16]. In addition, researchers have found a tumour growth rate of approximately 5 mm per year; thus, a 6-month follow-up is important for high-risk women with a germline mutation having a small enhancing lesion on MR imaging [17]. Contrastingly, as the majority of our study population were newly diagnosed breast cancer patients receiving systemic chemotherapy or endocrine therapy to reduce second breast cancer occurrence, short-term follow-up imaging for BI-RADS category 3 lesions detected on preoperative MRI might not be beneficial. Moreover, although 7.8% (49/626) of our

population had a familial history of breast cancer or were BRCA mutation carriers, no cancer was found in this population. This might have been associated with the effect of adjuvant therapy.

All detected cancers from BI-RADS category 3 lesions in our study were node negative T1 invasive cancers (median tumour size, 0.6 cm; range, 0.1–1.0 cm) or ductal carcinoma in situ (DCIS), which is comparable to the results of other studies. In addition, there was no difference in malignancy rate according to the lesion type on MRI in our study. Of the five cancers, three presented with a focus, one presented with a mass and one presented with NME. Although Grimm et al. reported that non-mass enhancements assessed as BI-RADS category 3 were significantly more likely to be malignant [9], other previous studies found that no significant morphological characteristics were predictive of malignant BI-RADS category 3 lesions on MR imaging [7, 8, 10, 11]. In our study, no cancer was found in the lesions presenting with multiple foci. Thus, as a previous study recommended [12], when the multiple foci in our study had been re-classified as BI-RADS

category 2, the frequency rate changed from 13.4% (683/5,110) to 7.6% (388/5,110); this is in line with recent BI-RADS Atlas recommendations that the frequency of BI-RADS category 3 should be less than 10% [14].

Our study has several limitations. First, because this was a retrospective study from a single institution and a relatively small number of patients with very small number of malignant cases were included, we cannot draw a solid conclusion. Second, follow-up MR imaging was not routinely performed in our study. If correlative findings were shown on mammography and US at the time of BI-RADS category 3 diagnosis, follow-ups were performed with mammography or US.

In conclusion, annual follow-up rather than short-term follow-up might be adequate for BI-RADS category 3 lesions detected on preoperative MRI based on the low malignancy rate, long interval between lesion detection and cancer occurrence, and early stage of detected cancers identified in this study. In addition, our results confirmed that although lesions with bilateral multiple foci exhibited several prominent foci or asymmetrical distribution, they were compatible with BI-RADS category 2 assessment. Considering the cost and availability of MR examinations, the use of BI-RADS category 3 on preoperative MR imaging should be further restricted.

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