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# Added value of contrast-enhanced breast MRI in patients with pure microcalcifications in biopsy decision-making

*Corresponding Author: Jianjuan Lou

Email: loujianjuan@sina.com

*Jianjuan Lou[1]*; Haiyan Gong[2]*

[1]Department of Radiology, The First Affiliated Hospital with Nanjing Medical University, China.

[2]Department of Ultrasound, The First Affiliated Hospital with Nanjing Medical University, China.

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## Abstract

**Purpose:** we aimed to explore the potential of 3.0T Contrast Enhanced MR (CE-MR) for differentiating benign and malignant microcalcifications, therefore to avoid unnecessary biopsy in the setting of pure microcalcifications.

**Methods:** From January, 2010 to March 2018, 135 lesions presenting as pure mammographic microcalcifications were enrolled. They were classified according to Breast Imaging Reporting and Data System (BI-RADS) on mammography, referred to as BI-RADS initial. Then, CE-MR images were retrospectively analyzed to determine whether there was a correlate enhancement on the corresponding area and a final BI-RADS assessment category (BI-RADS initial) was made. Based on pathological results, CE-MRI enhancement was compared between both benign and malignant groups. Univariate analysis was used for odd ratio calculation. Sensitivity, specificity, accuracy, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for BI-RADS final were calculated for the population. ROC analysis and area under the CE-MRI enhancement was compared between both groups. Univariate analysis was used for odd ratio calculation.ve (AUC) comparison were conducted to evaluated the performance of BI-RADS initial and BI-RADS final.

**Results:** There were 90 benign and 45 malignant lesions. The odds ratio of MRI enhancement for malignancy was 26.645. The sensitivity, specificity, PPV and NPV and accuracy, of BI-RADS final for the population were 97.78(44/45), 52.22%(47/90), 50.57%(44/87), 97.92%(47/48), 61.41%.

**Conclusion:** CE-MRI could offer some valuable information as whether a microcalcification lesion should undergo biopsy immediately.

## Introduction

As is known to all, mammography screening has decreased breast cancer morbidity and mortality worldwide since its wide availability. Some breast cancer, like [1] Ductal Carcinoma in Situ (DCIS) manifests microcalcifications on mammography. American College of Radiology (ACR) advocates that microcalcifications be classified as BI-RADS 4A or more suspicious undergo breast biopsy, with a PPV of 3-10%, 10-50%, 50-95%, over 95%, respectively [2]. In particular, when a lesion is classified as BI-RADS 4A, it means that more than 90% of people have to undergo an unnecessary procedure, resulting in patient discomfort and medical resource waste. A meta-analysis emphasized that a large proportion of biopsies of mammographic microcalcifications yielded benign results and therefore, potentially could have been avoided [3].

With the increasing use of mammography screening globally, purer microcalcifications are identified leading to more biopsies. However, mostly microcalcifications are found in benign lesions, such as adenosis, fibrocystic changes, fat necrosis, rarely granulomatous inflammation, et al [3]. It is unnecessary for these benign lesions to be surgically resected. MRI, though not a first-line choice, provides the highest sensitivity for breast cancer detection, reportedly to be 71%-100%. Many studies have been conducted, attempting to find the relationship between microcalcifications and correlation on CE-MR, but consensus was not reached [3-5]. In this study we aimed to evaluate the added value of 3.0T MRI to pure microcalcifications to help surgeons determine whether MRI could help avoid unnecessary biopsies in patients with pure microcalcifications.

## Methods

This retrospective study was approved by the Institutional Review Board. The decision number of our ethics committee approval was 2025-SRFA-085. We retrospectively reviewed the electronic medical record of wire-localization procedures in our department for pure microcalcifications from January 2011 to March 2018. There were 523 patients totally, among whom a subset of 163 patients was selected for availability of both mammography and MRI. Furthermore, 14 patients were excluded in that the time interval between mammography and MRI scan or between MRI scan and localization procedure exceeded one month; 27 patients were excluded for accompanied signs on mammography, such as mass, architectural distortion or asymmetry. Finally, 122 patients with 135 lesions presenting as pure mammographic microcalcifications were qualified for the study.

All the included patients underwent targeted resection surgery with localized wire. The removed specimens were imaged by a mammography unit to confirm the presence of microcalcifications. If absence of microcalcifications, an extended surgery was performed until the index microcalcifications were removed.

Mammographic images were obtained on a Mammography unit (Selenia, Hologic, USA) routinely with the craniocaudal and oblique mediolateral projection. The exposure parameters were automatically adjusted according to the detected breast density. Data were transferred to a specialized work station for interpretation.

MR imaging diagnostic studies were performed with a 3.0T MRI unit (Magnetom Trio, Siemens, Germany) and a dedicated 8-channel phased-array breast coil. Patients were in a prone position. T1WI scans were done before and after an intravenous administration of contrast agent (Magnevist, Schering, Germany) five times repeatedly. We employed a three-dimensional gradient-echo sequence with a repetition time: 4.23 ms, an echo time: 1.23 ms, a flip angle: 10°, a field of view: 340 mm* 340 mm, a matrix: 448*295, slice thickness:0.9mm, gap: 0 mm. Contrast agent was administered at a dosage of 0.1 mmmol/kg body weight at 3 ml/sec, followed by 20ml saline flush with a power injector. Sagittal or coronal acquisitions were obtained with reformats as appropriate.

Two breast imaging radiologists, with 5- or 10-years' experience in breast imaging interpretation were responsible for both mammographic and MR images. They were blinded to the clinico-pathological information. All image data were obtained in consensus.

First, the radiologists reviewed the breast mammography and recorded the shape, distribution of microcalcifications, based on which a BI-RADS initial category was made. At the moment, both radiologists had no access to the MR images. Next, both radiologists retrospectively analyzed MR images. During this period, they had access to mammography in order to precisely localize the microcalcification areas on MR images, but could not change the already-made BI-RADS initial category. BPE was determined on the first subtraction MIP images as minimal, mild, moderate and marked. Enhancement in the microcalcification territory on any phase was considered to be MRI positive. Enhancement outside the microcalcification territory or no enhanced correlation was regarded as MRI negative. When a symmetric enhancement was identified in both breasts, it was believed to represent BPE even if there were microcalcifications. MRI positivity made the BI-RADS final upgraded from 3,4A,4B,4C to 4A,4B,4C, 5, respectively. MRI negativity resulted in the BI-RADS final downgraded from 4C,4B,4A to 4B,4A,3 with the exception of 3, which remained unchanged in the absence of an MRI correlate.

The pathological findings of all surgical excisions were recorded at our hospital. Histological diagnoses were made by pathologists who specialized in breast pathology. For each case, we searched the pathological database to identify the final diagnosis. High risk lesions, such as atypical ductal hyperplasia, sclerotic adenosis were regarded as benign in the study. Clinical data were collected to through eletronic medical records to extract patient age, family or personal history of breast or ovary cancer and clinical manifestations.

### Statistical analysis

Continuous variables following normal distribution were presented in mean ±standard deviation. Categoric variables were reported as numbers and percentages. BI-RADS assessment category of 4A,4B,4C 5 was considered positive for malignancy with both BI-RADS final and BI-RADS initial. Univariate analysis was used to calculate Odds Ratio (OR) of MRI for malignancy. A Receiver Operating Characteristic (ROC) curve analysis was done to compare the performance of BI-RADS initial versus BI-RADS final. Sensitivity, specificity, PPV, NPV, accuracy for BI-RADS final were calculated, respectively. P value less than 0 .05 was considered to indicate a significant difference.

## Results

There were 122 patients with 135 pure microcalcification lesions meeting the inclusion criteria. One patient had three microcalcification areas, eleven patients had two microcalcification areas, and 110 patients had one microcalcification areas. The patient age were 45.9±8.3ys. Among the 122 patients, 77 were premenopausal, 40 were postmenopausal, and the rest five were unknown for menstrual status. Twenty-one patients had a high risk, including a history of personal breast cancer and/or family breast cancer. Mammography was taken for screening in 55 patients, for palpable or ultrasound detected mass in 60, for nipple discharge or eczema in five, and for breast pain in two (Table 1).

Pathological analysis revealed 90 benign lesions (33.3%) and 45(67.4%) malignant lesions. Malignant lesions included 25 pure DCIS, 18 cases of Invasive Ductal Carcinoma (IDC) mixed with DCIS and one IDC only. Benign lesions included adenosis, fibrocystic change, fibroadenoma, intraductal papilloma, ductal dilation, usual ductal hyperplasia, atypical ductal hyperplasia,

sclerotic adenosis, mucocele-like lesions, fat necrosis, et al.

On mammography, pure microcalcifications were classified as BI-RADS 3 in 21(15.6%), BI-RADS 4A in 65 (48.1%), BI-RADS 4B in 40 cases (29.6%), BI-RADS 4C (6.7%) in nine. Even though 19 lesions were BI-RADS intial 3 category, the patients insisted on surgery due to anxiety.

In the BI-RADS initial 3 group,6 of 21 lesions was upgraded to 4A, which were false positive. In the BI-RADS initial 4A group,33/65 were downgraded to BI-RADS final 3 according to CE-MR. Among them only one pathologically proved malignant. The rest 32 lesions were upgraded with 13 proved malignant. More lesions of BI-RAD initial 4B,4C were upgraded (25/40, 9/9), among which 21and 8 were malignant (Table 2).

ROC curve analysis revealed that the AUC were 0.776 (P<0.001, CI: (0.692-0.859) for BI-RADS initial and 0.890 (P<0.001, CI: 0.834-0.947) for BI-RADS final and the difference reached a statistical level (De-long test, P<0.05). In the study population, the sensitivity, specificity, PPV, NPV and accuracy for BI-RADS final were calculated to be 97.78(44/45), 52.22%(47/90), 50.57%(44/87), 97.92%(47/48), 61.41% (Figure 1).

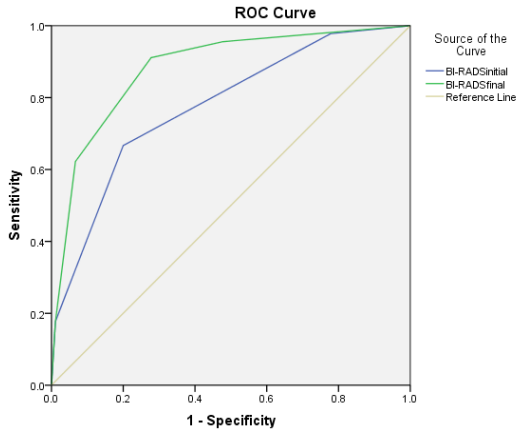


**Figure 1:** Diagnostic performance of BI-RADS initial and BI-RADS final with the AUC of 0.776 and 0.890, respectively.

**Table 1:** Characteristics of the 135 Lesions in 122 patients.

| Characteristics | Variable |
|---|---|
| Age | 45.9±8.3 ys |
| Menstrual status | |
| premenopausal | 77(63.1%) |
| postmenopausal | 40(42.8%) |
| unknown | 5(4.1%) |
| Personal or family history of breast cancer | |
| present | 21(17.2%) |
| absent | 101(82.8) |
| MG indications | |
| screening | 55(45.1%) |
| palpable or ultrasound-detected mass | 60(49.1%) |
| nipple abnormality | 5(4.1%) |
| Breast pain | 2(3.3%) |
| BI-RADSinitial | |
| 3 | 21(15.5%) |
| 4A | 65(48.1%) |
| 4B | 40(29.6%) |
| 4C | 9(6.7%) |
| BPE | |
| Minimal or mild | 87(64.4%) |
| Moderate or marked | 48(35.6%) |
| BI-RADSfinal | |
| 3 | 48(36.3%) |
| 4A | 21(14.8%) |
| 4B | 32(23.7%) |
| 4C | 25(18.5%) |
| 5 | 9(6.7%) |
| Histology of all lesions | |
| benign | 90(66.7%) |
| malignant | 45(33.4%) |
| Pure DCIS | 25(29.3%) |
| IDC+DCIS | 19(14.1%) |
| Pure IDC | 1(2.2%) |

BI-RADS: Breast Imaging Reporting and Data System; BPE: Background Parenchymal Enhancement; IDC: Invasive Ductal Carcinoma; DCIS: Ductal Carcinoma in situ.

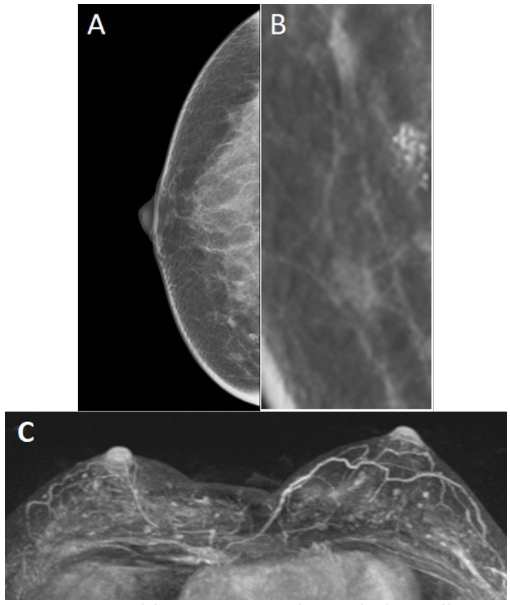


**Figure 2:** 39-year-old woman with pathologically confirmed fat necrosis. **(A)** Mammographic craniocaucal view showed grouped pleomorphic microcalcifications in the inner aspect of the right breast. **(B)** Magnified image demonstrated pleomorphic microcalcifications. **(C)** No definitive abnormal enhancement in the correlated territory was seen on MIP image.

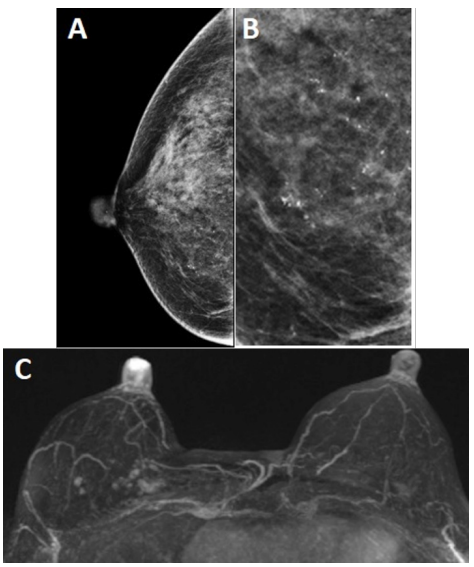


**Figure 3:** 58-year-old patient with pathologically confirmed ductal carcinoma in situ with concurrent Paget's disease. **(A & B)** Mammographic craniocaudal view and magnified image showed multiple pleomorphic microcalcifications in the inner aspect of the right breast. **(C)** MIP projection of the breast revealed nonmass like enhancement in the corresponding territory and nipple enhancement.

**Table 2:** BI-RADS final and BI-RADS initial and upgrade and downgrade rate.

| BI-RADS final | Total | Benign | Malignant | BI-RADS initial | Total | Benign | Malignant | Upgrade rate |
|---|---|---|---|---|---|---|---|---|
| | 135 | 90 | 45 | | 135 | 90 | 45 | |
| 3 | 48 | 47 | 1 | 3 | 21 | 20 | 1 | 6/21(28.57%) |
| 4A | 21 | 18 | 3 | 4A | 65 | 51 | 14 | 32/65(49.23%) |
| 4B | 32 | 19 | 13 | 4B | 40 | 18 | 22 | 25/40(62.5%) |
| 4C | 25 | 5 | 20 | 4C | 9 | 1 | 8 | 9/9(100%) |
| 5 | 9 | 1 | 8 | | | | | |

**Table 3:** MRI negative breast carcinoma summary.

| | Age (yr) | Pathologic results | Grade | Size (cm) | BPE | BI-RADS initial | BI-RADS final |
|---|---|---|---|---|---|---|---|
| 1 | 46 | DCIS | 3 | 1.2 | marked | 4B | 4A |
| 2 | 54 | DCIS | 1 | 0.2 | mild | 4A | 3 |
| 3 | 47 | DCIS | 3 | 0.8 | moderate | 4B | 4A |

In the 72 MRI positive lesions, 42 lesions were malignant while in the 62 MRI negative lesions, three lesions were malignant (Table 2). Univariate analysis revealed a significant difference (P<0.001) and the odds ratio was 26.645 (CI: 7.639-92.944) (Figures 2,3). Among the 72 MRI positive lesions, nonmass-like enhancement pattern was found in 59, mass lesion was seen in 11, mixed pattern was detected in two. Thirty-five of 59 nonmass-like enhanced lesions, 2 of 11 mass lesions, both two mixed pattern lesions were malignant. However, three lesions without a CE-MRI correlate proved malignant. All were pure DCIS lesions with the size of 1.2 cm, 0.2 cm, 0.8 cm. The 0.2 cm low grade DCIS arose from the breast with mild BPE. The other two arose in breasts with moderate or marked BPE. Their mammographic BI-RADS assessment categories were BI-RADS 4A,4B.

## Discussion

The mechanism(s) producing microcalcifications remain largely undefined, although aberrant secretion and necrosis have been hypothesized to contribute to their formation [8]. Mammography screening has largely decreased the morbidity and mortality of breast cancer by detecting microcalcifications in early breast cancer. However, many benign lesions also manifest as suspicious microcalcifications (heterogenous coarse, amorphous, pleomorphic) [3,6] on mammography and patients may sustain unnecessary biopsy for that. On the other hand, calcium deposition in breasts takes a relatively long time in a progressive manner, especially for benign process. At the early stage of benign calcium deposition, microcalcifications may represent a diagnostic dilemma and high BI-RADS category may be assigned. This is supported by the fact that some incidentally found microcalcifications at microscopy are not identified on mammography in clinical work.

MRI, as the most sensitive imaging modality, has been accepted in many circumstances, such as high-risk population screening, inderterminate ultrasound or mammographic findings, breast cancer staging, guidance for treatment planning, and chemotherapy surveillance, et al. The sensitivity of MRI for breast cancer is reportedly to be extremely high [7]. The present study was designed to explore the possibility of reduction in pure benign microcalcification-associated breast biopsy with the help of CE-MRI. Particularly, when multiple groups of microcalcifications are revealed, there is a dilemma that which one(s) should be biopsied because wire localization of each group is not feasible or practicable. Now some authors even questioned whether increased detection of microcalcifications led to over-investigation and over-diagnosis [9].

Our study showed that MRI-positive microcalcifications were more prone to be malignant with an OR value over 26. The finding was consistent with previous studies [10,11]. It can be readily understood pathologically as the fact that angiogenesis plays a key role in the development of carcinoma and its progression [12]. Carcinoma-associated neovascularity is more permeable than normal breast vascular structures, leading to contrast agent leakage into the extracellular space. Therefore, we hypothesized that if there was a correlate enhancement in the microcalcification area on CE-MR, there was a higher probability for the presence of malignancy.

A number of studies have focused on the diagnostic performance of MR imaging to distinguish between benign and malignant mammographic microcalcifications, but results varied substantially. So, breast MR imaging is currently not recommended for evaluation of mammographic microcalcifications [13]. When reviewing the previous studies, we found that most of them were performed on a 1.5T MRI unit and only a few were done on a 3.0T MRI unit. PPV for contrast enhanced MRI ranges between 15% and 50% and depends upon patient selection and MR interpretation algorithm. Among these articles, one was written by our team [14]. That study involved not only pure microcalcification cases, but also microcalcifications with mass, architectural distortion or asymmetry, while the present study excluded microcalcification cases with other signs. Our study design is different from those of previous studies as we focused on reducing the benign microcalcification-associated biopsy rate. The patients were in an upright position when taking mammography and in a prone position when taking MRI scan. When analyzing the MRI images, radiologists had access to mammography in order to judge whether the enhanced area was correlated with microcalcifications. Thus, knowledge of the presence of microcalcifications might make them more alert to any suspicious findings, which gave a reasonable explanation to the high sensitivity 97.78(44/45) on CE-MRI.

When mass lesions were focused on, 5 of 11 were false positive, which were diagnosed as BI-RADS 3 in one or 4A in four on mammography. On MRI, most of the five false-positive mass lesions demonstrated typical benign features (round or ovoid shape, circumscribed margin and persistent type TIC) [15]. Therefore, we believed that MRI morphology would have increased diagnostic performance of CE-MRI correlation. The suspicious microcalcifications of four BI-RADS 4A lesions could be explained by the presence of early stage of benign calcium deposition, during which the shape and distribution is not typical for benignity. In other words, the microcalcifications are not mature and will continue changes until its stability, manifesting classical benign features.

The study results was similar to previous studies [16,17]. According to the CE-MRI, if we had had only the BI-RADS final 4A or more suspicious lesions resected,33 of 65 lesions should have avoided the resection procedure, none of which was malignant with the cost of five additional BI-RADS initial 3 lesions being resected. Meanwhile, a BI-RADS initial 3 lesion was upgraded to BI-RADS final 4A, which eventually proved to be a small IDC. The sensitivity was high enough to identify the malignant lesions, while the high NPV of 97.92% (47/48) could make imaging follow up safe in patients with pure microcalcifications with BI-RADS final category 3.

Although few literatures pay attention to the false-positive lesions of breast, they do have an impact on the accuracy of breast MRI. In the present study, most of false-positive cases were fibrocystic changes and adenosis. In these cases, microcalcifications usually lay in tubules and acini at microscopy, much less frequently in stroma. The former calcium deposition site is postulated to be secretory in pathologists' perspective. Among the benign microcalcification lesions, 31(31/90,34.44%) showed a CE-MRI correlate, which meant that in some benign lesions, vascular changes also occur, which was reported by other authors [13,18]. And most of them were nonmass like enhancement. We support the idea that nonmass like enhancement represents a challenging subgroup at diagnostic breast MRI [19]. This contributes to the relatively lower PPV. However, the PPV did increase from 38.60(44/114) for BI-RADS initial to 50.57% for BI-RADS final.

Three malignant cases were not detected on MRI (Table 3). As a basic BI-RADS initial category was taken in account, even if there was absence of a MRI correlate, only one was missed based on BI-RADS final assessment category. It was a small DCIS (2 mm) with BI-RADS initial 3 occurring in a breast with mild BPE. Such lesion is the least aggressive, and its undetectability could be acceptable without causing serious problems if imaging follow-up at an interval of six months is available; This made the BI-RADS final reliable for biopsy decision making. The other two MRI negative lesions were believed to be due to moderate or marked BPE. BPE is considered to be a key impactor on the higher abnormal interpretation rate [8]. A vast majority of DCIS demonstrate nonmass like enhancement on MRI [20]. When high degree of BPE exits, nonmass like enhancement pattern of DCIS might be interpreted as BEP. This could explain the two missed cases in our study.

### Limitations

There are some limitations to the present study. First, this is a retrospective study. Secondly, the corresponding site of microcalcifications on MRI was subjectively judged in consensus. No marker was placed. Second, we solely relied on the absence or presence of enhancement on CE-MRI for statistical analysis. The study is more feasible when radiologists are inexperienced in MRI interpretation . In some circumstances, such as fibroadenomas associated immature microcalcifications, features of shape and margin is quite valuable. Third, malignancies were not analyzed according to molecular subtypes. Whether MRI missed lesions have association with molecular subtypes needs to be explored with a much larger population.

## Conclusion

In conclusion, breast microcalcifications only with a correlate on CE-MR were more likely to represent malignancy. Further, we believed that breast biopsy could be avoided in some selected patients, especially with BI-RADS 4A on mammography. MRI correlation should be made in the second week of menstrual cycle to minimize the BPE impact.

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