



Breast Imaging

Malignancy rates of stereotactic biopsies of two or more distinct sites of suspicious calcifications in women without known breast cancer

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ABSTRACT

Objective: To determine the malignancy rate in women without a concurrent breast cancer diagnosis at presentation who underwent stereotactic biopsies of distinct sites of suspicious calcifications.

Methods: This retrospective study included 280 women without a concurrent breast cancer diagnosis who underwent 587 stereotactic biopsies of two or more distinct sites of suspicious calcifications in one or both breasts at our institution from 2010 to 2015.

Results: The overall malignancy rate was 27.9% (78/280, 95% CI, 22.7%–33.5%) at the patient level and 18.7% (110/587, 95% CI, 15.7%–22.1%) at the lesion level. Eighteen had invasive cancers (mean [range] diameter, 0.5 cm [0.1–1.7]; six grade I, ten grade II, two grade III), one of whom had multifocal and another bilateral malignancy. Sixty had ductal carcinoma in situ. Of the 171 with all calcifications of the same morphology, 139 (81.3%) had all calcifications in the same pathology category (benign, high-risk, or malignant).

Conclusion: The malignancy rate is substantial in women who undergo stereotactic biopsies of two or more distinct calcification sites. Given the nearly 20% rate of dissimilar histopathology between calcification sites with similar morphology, if only one site is biopsied and results in a malignant pathology, biopsy of the additional calcifications is warranted. Even if the pathology result of the one site biopsy is benign, biopsy of additional sites may perhaps still be necessary.

1. Introduction

Mammography is used as a first-line breast cancer screening tool, and calcifications are one of the most common findings on mammography [1]. Calcifications can be associated with invasive and in situ cancers [1–3] but also with benign lesions [4,5], and the histopathologic properties of calcifications from benign and malignant breast lesions can overlap [6–8]. Management of breast calcifications can be difficult. In an effort to help radiologists standardize the description and assessment of breast calcifications, the American College of Radiology developed the Breast Imaging Reporting and Data System (BI-RADS), which categorizes calcifications as benign, probably benign, or suspicious on the basis of calcification morphology and distribution [2]. However, both benign and malignant lesions can produce mammographically suspicious calcifications [9–13]. Hence, the predictive value of the BI-RADS descriptors is limited with a likelihood of malignancy from 13% to 70% [2].

It is not uncommon for a woman to have two or more sites of calcifications in the same or both breasts with suspicious morphology according to the BI-RADS criteria. There are a few studies on management of a large area of contiguous calcifications. Raj and colleagues suggested that a single biopsy of segmental calcifications instead of two stereotactic biopsies of anterior and posterior aspects of the suspicious calcifications is adequate for diagnosis [14], but 100% histopathological agreement of the anterior and posterior biopsies was not observed by another study (87% agreement in that study) [15]. Management of women with two or more distinct sites of suspicious calcifications is even less studied.

The objective of this study was to determine the malignancy rate in women without a concurrent breast cancer diagnosis at presentation who underwent stereotactic biopsies of two or more distinct sites of suspicious calcifications.

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2. Subjects and methods

2.1. Patient selection

This HIPAA-compliant study was approved by our Institutional Review Board, and the requirement for informed consent was waived.

An institutional database was searched to identify women who underwent stereotactic core biopsies of two or more distinct non-contiguous sites of calcifications in one or both breasts at our institution from September 1, 2010, through September 30, 2015. The calcifications had to be present on the same diagnostic mammogram. All the biopsies were performed on the same day or within 3 months of one another. At our institution, within the study time period, when a woman presents with two sites of suspicious calcifications, generally both sites of calcifications will be recommended for stereotactic biopsies on the same day. However, when a woman presented with three or more sites of suspicious calcifications, while some breast imagers still recommended all three sites to be biopsied on the same day, others suggested the management of the additional calcifications to be contingent on the biopsy results of the first two sites. Women who had a known current breast cancer diagnosis when they presented for the diagnostic work-up were excluded, as were women who underwent two or more stereotactic biopsies of the opposite extents of contiguous calcifications. A total of 280 women who underwent 587 stereotactic biopsies met the selection criteria and constituted the study cohort.

2.2. Review of imaging features

All the diagnostic mammograms obtained prior to the stereotactic guided core biopsies were reviewed by one of three fellowship-trained breast-imaging radiologists. All calcifications were evaluated by orthogonal spot compression magnification views at the time of original imaging. Specimen radiographs and postprocedure mammograms were also reviewed to confirm sampling of the targeted calcifications.

Discrete sites of calcifications were defined as sites of calcifications separated by at least 1 cm without any intervening calcifications. Each discrete site of calcifications was reviewed independently. Each site of calcifications was considered one lesion. Calcification location, morphology, and distribution were recorded according to the fifth edition of the BI-RADS lexicon [2], and the largest diameter of each site of calcifications was recorded. In the fifth edition of the BI-RADS lexicon, punctate is classified as a subset of round, but in this manuscript, we have used “punctate” to precisely convey the morphology of the calcifications. Based on the fifth edition of the BI-RADS lexicon, suspicious calcifications can be further subcategorized as 4A: low suspicion for malignancy; 4B: moderate suspicions for malignancy (i.e. amorphous, coarse heterogeneous, fine pleomorphic calcifications); 4C high suspicion for malignancy (i.e. fine linear or fine linear branching calcifications).

2.3. Collection of clinical data

The following clinical data were collected from the electronic medical records: age at time of diagnostic mammography; biopsy date; biopsy device gauge; number of core biopsy samples; any subsequent mastectomy, lumpectomy, or excision; size of any invasive cancer on the surgical specimen; and personal history of breast cancer.

2.4. Biopsy method

All stereotactic guided core biopsies were performed using a 9-gauge vacuum-assisted biopsy device (Suros ATEC, Hologic, Bedford, MA). The number of core samples ranged from 3 to 22 (median, 7; mean, 8). In all patients, targeted calcifications were retrieved. In three patients, 20 or more core samples were obtained because the targeted calcifications were not retrieved on the first attempt.

2.5. Pathology

All pathology reports were reviewed. On the basis of review of these reports, calcifications were categorized as benign, high-risk, or malignant. High-risk lesions included atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, flat epithelial atypia, radial scar, atypical apocrine metaplasia, and atypical papillary lesion. When there was a discrepancy between the pathology category (benign, high-risk, or malignant) for the stereotactic core biopsy specimen and the final surgical pathology category, the more severe tissue diagnosis was recorded. When invasive cancer was multifocal or multicentric on the lumpectomy or mastectomy specimen, the size of the largest focus was used. Radiology and pathology concordance was assessed for every lesion.

2.6. Statistical analysis

For quantitative data, range and median were reported. For qualitative data, frequencies and percentages were reported. Fisher exact tests were used to compare proportions and to assess associations. Wilcoxon rank-sum test was used to compare largest dimensions between malignant and benign calcifications. Exact binomial 95% confidence interval (CI) was computed for proportions. All tests were two-sided, and a p value of 0.05 was applied as a threshold for statistical significance. Statistical analysis was carried out using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Characteristics of the study population and calcifications

The 280 women (587 lesions) in the study cohort ranged in age from 28 to 85 years (median, 54 years). Fourteen women (5.0%) were 39 years of age or younger, 74 (26.4%) were 40 to 49 years of age, 159 (56.8%) were 50 to 69 years of age, and 33 (11.8%) were 70 years of age or older. Fifty-six of the 280 women (20.0%) had a prior history of breast cancer.

3.2. Malignancy rates at the lesion level

Malignancy rates at the lesion level are presented in Table 1. The histopathology of all biopsied lesions was deemed imaging-concordant. The overall malignancy rate was 18.7% (110/587; 95% CI: 15.7%–22.1%). The malignancy rate was 18.8% (96/510) for lesions

Table 1

Malignancy rates at the lesion level by number of biopsy sites, calcification morphology, and calcification distribution.

Group	No. of lesions with malignant pathology/no. of lesions (%)	P by Fisher's exact test
All lesions	110/587 (18.7)	
Number of biopsy sites		> 0.99
2	96/510 (18.8)	
3 or 4	14/77 (18.2)	
Calcification morphology		< 0.0001
Amorphous	36/285 (12.6)	
Coarse heterogeneous	34/230 (14.8)	
Fine pleomorphic	32/51 (62.7)	
Fine linear/linear branching	8/18 (44.4)	
Punctate	0/3 (0)	
Calcification distribution		< 0.0001
Grouped	81/490 (16.5)	
Regional	5/46 (10.9)	
Segmental	17/27 (63.0)	
Linear	6/19 (31.6)	
Diffuse	1/5 (20.0)	

biopsied as part of two-site biopsy and 18.2% (14/77) for lesions biopsied as part of three- or four-site biopsy ($p > 0.99$).

The median largest lesion diameter was 0.7 cm (range, 0.1–9.4 cm). Of the 587 lesions, 104 (17.7%) were malignant, 96 (16.4%) were high risk, and 387 (65.9%) were benign. Six of the 96 high-risk lesions (6.3%) were upgraded at excision, for a final total of 110 malignant lesions. The malignant lesions were significantly larger than the benign lesions (median largest lesion diameter, 1 cm [range, 0.1–7.8 cm] vs 0.7 cm [range, 0.1–9.4 cm]; $p < 0.0001$ by Wilcoxon rank-sum test). The malignancy rate was 12.6% (36/285) for amorphous calcifications, 14.8% (34/230) for coarse heterogeneous calcifications, 62.7% (32/51) for fine pleomorphic calcifications, 44.4% (8/18) for fine linear or linear branching calcifications, and 0% (0/3) for punctate calcifications ($p < 0.0001$). The highest malignancy rate was observed in calcifications in a segmental distribution (63.0%; 17/27), and the lowest malignancy rate was observed for calcifications in a regional distribution (10.9%; 5/46). The three cases of punctate calcifications in two patients include punctate calcifications in a linear distribution (in one patient), and two groups of punctate calcifications (in one patient) have increased in number from a comparison mammogram five years ago.

3.3. Malignancy rates at the patient level

Malignancy rates at the patient level are presented in Table 2. The overall malignancy rate was 27.9% (78/280; 95% CI: 22.7%–33.5%). Eighteen women had invasive cancers. Of these women, one had a multifocal malignancy, and one had a bilateral malignancy. The invasive tumors ranged in size from 0.1 cm to 1.7 cm (mean, 0.5 cm); six were grade I, ten were grade II, and two were grade III. Sixty women had ductal carcinoma in situ.

The malignancy rate was 27.5% (70/255) in women who underwent biopsy of two sites of calcifications and 32.0% (8/25) in women with biopsy of three or four sites of calcifications ($p = 0.64$). The malignancy rate was 31.1% (56/180) in women with all calcifications in the same breast and 22.0% (22/100) in women with calcifications in both breasts ($p = 0.13$). The malignancy rate did not differ significantly by age group (Table 2).

The malignancy rate was lower in women with all calcifications of the same morphology (21.1%; 36/171) than in women with calcifications of different morphologies (38.5%; 42/109) ($p = 0.002$). Among the 171 women with all calcifications of the same morphology, the malignancy rate was 20.2% (19/94) for women with amorphous calcifications (Figs. 1, 2), 15.2% (10/66) for women with coarse heterogeneous calcifications, and 77.8% (7/9) for women with fine pleomorphic calcifications; the one woman with fine linear calcifications and the one woman with punctate calcifications did not have

Table 2
Malignancy rates at the patient level by number of biopsy sites, location of calcifications, patient age group, and calcification morphology.

Group	No. of patients with malignancy/ no. of patients (%)	P by Fisher's exact test
All patients	78/280 (27.9)	
Number of biopsy sites		0.64
2	70/255 (27.5)	
3 or 4	8/25 (32.0)	
Location of calcifications		0.13
Same breast	56/180 (31.1)	
Both breasts	22/100 (22.0)	
Patient age group		0.14
39 years or younger	1/14 (7.1)	
40–49 years	17/74 (23.0)	
50–69 years	48/159 (30.2)	
70 years or older	12/33 (36.4)	
Calcification morphology		0.002
Same morphology	36/171 (21.1)	
Different morphology	42/109 (38.5)	

malignancy ($p = 0.001$). When comparing the number of fine linear and pleomorphic calcifications at the lesion level between women with calcifications of different morphologies and those with calcifications of the same morphology, there were 16/231 (6.9%) fine linear and 32/231 (13.9%) fine pleomorphic calcifications in women with calcifications of different morphologies versus 2/356 (0.6%) fine linear and 19/356 (5.3%) fine pleomorphic calcifications in women with calcifications of the same morphology.

Of the 171 women with all calcifications of the same morphology, 139 (81.3%) had all calcifications in the same pathology category. Of the 64 women who had all calcifications of the same morphology and all calcifications in the same quadrant, 54 (84.4%) had all calcifications in the same pathology category. Among the 32 women with morphologically similar calcifications but different pathology findings, 25% (8/32) of those had one site benign and the other site(s) malignant (Table 3).

Of the 109 women with calcifications of varying degrees of suspicion for malignancy, based on BI-RADS calcifications subcategories (4A, 4B, 4C), when the BI-RADS 4C, fine linear/fine linear branching calcifications are biopsy-proven non-malignant (in 8 women), the other morphologically less suspicious BI-RADS 4A/B calcifications also have non-malignant biopsy results.

4. Discussion

In this study, we found that the malignancy rate in women without a concurrent breast cancer diagnosis who underwent stereotactic guided biopsies of two or more distinct sites of suspicious calcifications was 27.9% (78/280) at the patient level and 18.7% (110/587) at the lesion level. The malignancy rate did not differ significantly between women who underwent biopsy of two versus three or four sites of calcifications, nor did it differ significantly between women with unilateral versus bilateral calcifications. Additionally, there was no significant difference in malignancy rates among different age groups.

Grimm and colleagues [16] found a high malignancy rate of 33.8% (78/231) in women age 70 years or older undergoing stereotactic guided biopsy of calcifications. Similarly, in our study cohort, the malignancy rate of women age 70 years or older was 36.4% (12/33).

The malignant lesions in our series were larger in size than the benign lesions by Wilcoxon rank-sum test. However, the size ranges of the malignant and benign lesions overlapped, which makes it difficult to use lesion size as a predictor of malignancy.

Majewski and colleagues reported that in 123 patients with a known high-risk lesion who underwent 158 secondary presurgical imaging-guided percutaneous biopsies, 96.8% of the biopsies (153/158) yielded additional high-risk and/or benign findings [17]. Other authors previously suggested that when a woman has multiple sites of amorphous calcifications, biopsy of one site can reliably predict the pathology result of the others [9]. In our cohort, 81.3% of women with all calcifications of the same morphology had all calcifications in the same pathology category, and the percentage was slightly higher (84.4%) if the morphologically similar calcifications were all in the same quadrant. Similar results were reported by Oligane and colleagues [18], who found that stereotactic biopsies of multiple groups of amorphous calcifications in the same quadrant showed the same results 76.9% of the time.

In our study cohort, women with calcifications of different morphologies were significantly more likely to be diagnosed with cancer than were women with all calcifications of the same morphology ($p = 0.002$). However, there were a larger number of fine linear (6.9%) and fine pleomorphic (13.9%) calcifications in women with calcifications of different morphologies compared to those in women with calcifications of the same morphology (0.6% and 5.3% respectively). Since fine linear and fine pleomorphic calcifications are known to have higher malignancy rates than amorphous and coarse heterogeneous calcifications, the larger proportion of fine linear and pleomorphic

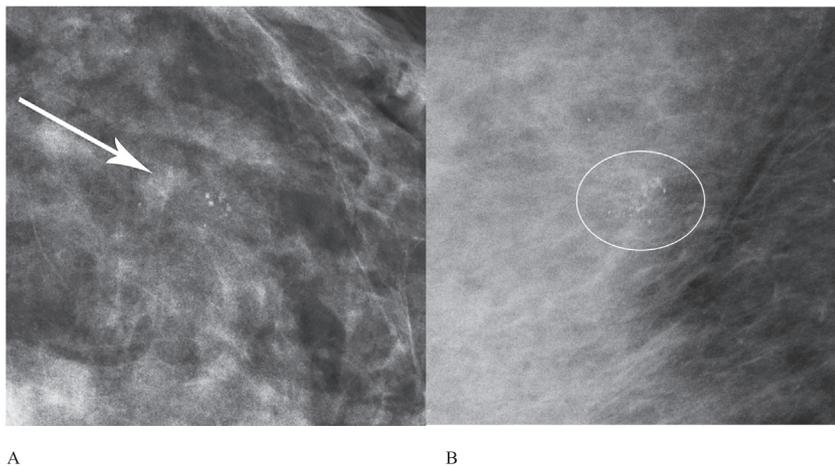


Fig. 1. Fifty-year-old woman with calcifications in both breasts.

Left craniocaudal magnification (A) and right craniocaudal magnification (B) mammograms showed grouped amorphous calcifications in both breasts. Stereotactic biopsy of the left breast calcifications (arrow) revealed benign fibrocystic change, and stereotactic biopsy of the right breast calcifications (circle) revealed ductal carcinoma in situ of intermediate grade.

calcifications in women with calcifications of different morphologies may explain this finding.

By using BI-RADS subcategories, when calcifications in the BI-RADS 4C subcategory have non-malignant pathology, calcifications in the BI-RADS 4A/B subcategory in the same patient (8 women) also have non-malignant pathology. However, in our study cohort, the number of women with non-malignant BI-RADS 4C and BI-RADS 4A/B calcifications is very small. Therefore, a larger study cohort to validate this finding is needed.

According to BI-RADS lexicon, the likelihood of malignancy is 70% for fine linear/linear branching, 29% for fine pleomorphic, 21% for amorphous, and 13% for coarse heterogeneous calcifications [2]. A study by Kim and colleagues based on the fifth edition of the BI-RADS lexicon and limited to women with calcifications at a single site showed that the malignancy rate was 100% for fine linear/linear branching, 63.2% for fine pleomorphic, 17.8% for coarse heterogeneous and 7.9% for amorphous calcifications [11]. Our study showed that at the lesion level, the calcification morphology associated with the highest malignancy rate was fine pleomorphic calcifications, for which the malignancy rate was 62.7%, similar to the rate in the study by Kim and colleagues [11]. The malignancy rate for coarse heterogeneous calcifications in our study was 14.8%, similar to the rates presented in the fifth edition of the BI-RADS and reported by Kim and colleagues. The malignancy rate for amorphous calcifications in our study was 12.6%, which was similar to the rates in the Kim et al. study [11] and a recently reported study of amorphous calcifications, which showed a malignancy rate of 10.5% [18]. Our study included relatively small numbers of cases of fine linear/linear branching calcifications (18 cases) and punctate calcifications (3 cases). Hence, no definite conclusion can be

drawn about the findings with respect to those two morphologies. Interestingly, the malignancy rates for amorphous and fine pleomorphic calcifications at the lesion level (12.6% and 62.7%, respectively) were lower than the malignancy rates for amorphous and fine pleomorphic calcifications at the patient level in women who had all lesions of the same morphology (20.2% and 77.8%, respectively). The exact underlying cause is unclear. However, these findings seem to parallel the findings recently reported by another group; in their study, the malignancy rate for amorphous calcifications was 25% when belonging to multiple groups in the same quadrant versus 7% for a solitary group [18].

This study has a few limitations. First, it was a single-institution study at a tertiary cancer center, which raises the question whether the study results can be generalized to the community setting. Second, 20.0% of the study population had a prior history of breast cancer, although no significant difference in malignancy rate was observed between women with and without a prior history of breast cancer. Third, the study cohort included only those women who had two or more sites of stereotactic biopsies. Hence, there is a selection bias and cannot be generalized to all patients presenting with multiple sites of calcifications, though at our institution when a patient presents with two sites of suspicious calcifications, both sites are biopsied at the same time in the majority of cases.

In conclusion, we found that the malignancy rate was 27.9% in women who underwent stereotactic guided biopsies of multiple distinct suspicious calcifications in the same or both breasts. When there were multiple distinct sites of similar-appearing suspicious calcifications, the calcifications were in the same pathology category in approximately 80% of patients; however, nearly 20% of patients with similar-

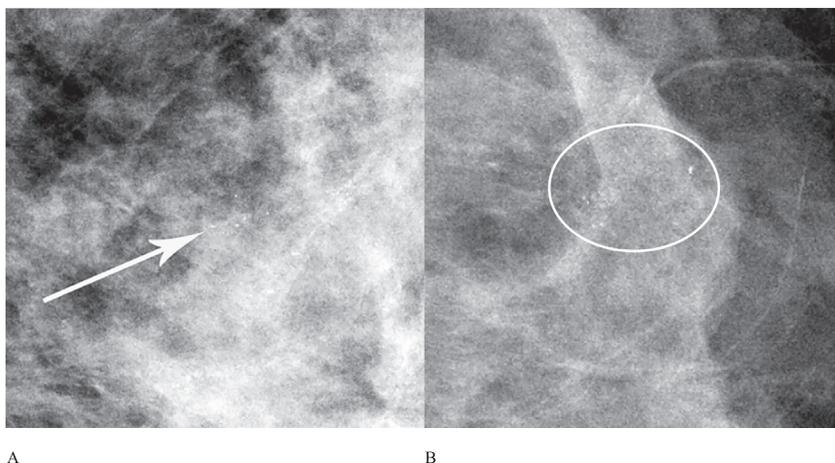


Fig. 2. Sixty-three-year-old woman with atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS) in the left breast.

On mammography, lateral magnification views of calcifications at 2 o'clock in the left breast (A) and 3 o'clock in the left breast (B) showed grouped amorphous calcifications. Stereotactic biopsy of the left breast 2 o'clock calcifications (arrow) revealed ADH (not upgraded at excision), and stereotactic biopsy of the left breast 3 o'clock calcifications (circle) revealed grade 1–2 DCIS.

Table 3
Details of women with morphologically similar calcifications but different pathologies.

Pathology	Benign & malignant (%)	Benign & high risk (%)	High risk & malignant (%)	Benign & malignant & high risk (%)	Total
2-Site biopsies	7/26 (26.9)	14/26 (53.8)	5/26 (19.2)	0/26 (0)	26
3-Site biopsies	1/5 (20.0)	1/5 (20.0)	2/5 (40.0)	1/5 (20.0)	5
4-Site biopsies	0/1 (0)	1/1 (100.0)	0/1 (0)	0/1 (0)	1
Total	8/32 (25.0)	16/32 (50.0)	7/32 (21.9)	1/32 (3.1)	32

appearing calcifications had calcifications of different pathology categories. Thus, in women with two or more sites of suspicious calcifications, if only one site is subjected to biopsy, resulting in a malignant pathology, biopsy of the additional calcifications is warranted. Even if the pathology result of the one site biopsy is benign, additional biopsy may perhaps still be necessary for the other sites.

Meeting presentation

Preliminary data were presented at the 2016 RSNA meeting.

Declaration of Competing Interest

Dr. Leung has served on the Scientific Advisory Board and Speakers' Bureau of Hologic, Inc. She has also served on the Speakers' Bureau of Fujifilm, Inc.

All the other authors have nothing to disclose.

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