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A New Method for Differentiating Benign and Malignant Pleomorphic Clustered Calcifications in Mammography

Mari Kikuchi[1,2], Hiroko Tsunoda[1], Tadashi Kaneshiro[3], Osamu Takahashi[4], Koyu Suzuki[5], Hideko Yamauchi[6], Taro Ichikawa[2] and Shin-ichiro Kumita[7]

[1]Department of Radiology, St. Luke's International Hospital
[2]Department of Radiology, Nippon Medical School Musashi Kosugi Hospital
[3]Center for Minimally Invasive Treatment, Nippon Medical School Musashi Kosugi Hospital
[4]Department of General Internal Medicine, St. Luke's International Hospital
[5]Department of Pathology, St. Luke's International Hospital
[6]Department of Breast Surgery, St. Luke's International Hospital
[7]Department of Radiology, Nippon Medical School Hospital

Abstract

Objective: Retrospective study to determine whether new mammography imaging characteristics can improve identification of an isolated cluster of coarse heterogeneous and fine pleomorphic calcifications as benign or malignant.

Materials and Methods: Institutional review board approval and informed consent were obtained. The study included 123 women (mean age, 50 years: age range, 34–79 years), in whom mammograms had found pleomorphic clustered calcifications, but without abnormal ultrasound findings and who underwent stereotactically-guided vaccum-assisted breast biopsy. Pleomorphic clustered calcifications were classified on the basis of 5 characteristics density, heterogeneity of density, number, heterogeneity of size, and distribution area size (DAS) of calcifications in the mediolateral oblique view (multiplication of the greatest length by the width of the total zone of clustered calcifications in mm^2), and correlated with pathological findings.

Results: The chi-square test showed significant differences in whether a calcification was malignant or benign only in terms of DAS of calcification (p 0.009). There were significant differences in the association with malignancy of a DAS of 32- to 55 mm^2 (p=0.023, odds ratio= 4.22), and the association more likely with a DAS of 56 mm^2 or larger (p=0.01, odds ratio=5.55) than with a DAS smaller than 18 mm^2 as a reference.

Conclusion: The DAS is a new and reliable variable for differentiating between benign and malignant pleomorphic clustered calcifications. The DAS improves diagnostic accuracy and is useful for determining whether to proceed with biopsies.
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Key words: mammography, pleomorphic clustered calcifications, stereotactically-guided vacuum-assisted breast biopsy

Correspondence to Mari Kikuchi, MD, Ph.D, Department of Diagnostic Radiology, National Cancer Center Hospital, 5–1–1 Tsukiji, Chuo-ku, Tokyo 104–0045, Japan
E-mail: markikuc@ncc.go.jp
Journal Website (http://www.nms.ac.jp/jnms/)

Introduction

Correctly evaluating benign and malignant calcifications identified on mammography for the early detection of breast cancer is important[1–4]. The Breast Imaging Reporting and Data System (BI-RADS) standardizes the description and management of findings of mammography, thereby facilitating communication between radiologists and referring physicians[5]. Calcifications identified with mammography are classified along a scale from benign to malignant on the basis of morphology and distribution.

Pleomorphic clustered calcifications are classified as more likely to be malignant in the BI-RADS, 3rd edition, published in 1998[6]. In the largest study to date, researchers found a 37% malignancy rate for pleomorphic clustered calcifications[7–9]. Approximately two-thirds of the microcalcifications identified in that study were described as clusters of pleomorphic calcifications. The term "pleomorphic" has been used to encompass a broad spectrum of calcification lesions.

The of BI-RADS, 4th edition (published in 2003)[10] refined microcalcification descriptors by dividing the former pleomorphic descriptor into 2 categories: coarse heterogeneous and fine pleomorphic. Coarse heterogeneous calcifications that are irregular, conspicuous, and generally greater than 0.5 mm in diameter are considered to be of intermediate concern. Fine pleomorphic calcifications vary in size and shape; those less than 0.5 mm in diameter are considered more likely to be malignant.

Nevertheless, we have encountered patients in routine clinical practice whose calcifications fail to fall neatly into a single BI-RADS category. Further data on individually clustered pleomorphic calcifications are needed, as is indicated in the Guidance Chapter of the BI-RADS, 4th edition[10].

The purpose of this study was to investigate other imaging criteria that might help differentiate benign and malignant calcifications.

Materials and Methods

This study was approved by institutional review boards, and written informed consent was obtained from all participants before stereotactically - guided vacuum-assisted breast biopsies (VAB).

The study included 123 patients who exhibited pleomorphic clustered calcifications on mammography but no abnormalities associated with the area of microcalcifications in ultrasound findings. From January 2004 through June 2012, we performed stereotactically - guided VAB to obtain pathological results for all subjects at 2 institutions.

Mammography was performed with a GE Senographe DMR, 800T (GE Medical Systems, Milwaukee, WI) or a Siemens MAMMOMAT Novation DR (Siemens Medical Systems, Erlangen, Germany). Screen-film mammogram were read from January 2004 through June 2008, and full-field digital mammogram were read from July 2008 through June 2012. Stereotactically - guided VAB was performed with a LORAD stereotactically guided system (A Hologic Company, Bedford, MA, USA) and a digital spot mammography system with subjects lying prone, or a Siemens MAMMOMAT Novation DR with subjects seated. All stereotactically - guided VABs were performed with an 11 G probe.

Interpreting the Mammography Findings

The mammograms of the 123 patients were independently reviewed by 2 diagnostic radiologists (with 8 and 24 years' experience in breast imaging and certified by the Central Committee on Quality of the Mammographic Screening in Japan) who had no knowledge of clinicopathologic findings. If the 2 readers reached different assessments, a consensus was reached through discussion.

The characteristics of the pleomorphic clustered calcifications identified were investigated retrospectively, and the calcifications were classified on the basis of 5 characteristics: density (amorphous, intermediate, high), heterogeneity of density (homogeneous, heterogeneous), number (less than 20, 20–35, 36 or greater) by quartiles divisions,

Table 1 Evaluated Aspects of Calcifications in Benign to Malignant Lesion

Total (n=123)			Benign (n=68)	Malignant (n=55)	P value
Mean age (SD), years			49 (10)	51 (10)	0.267
Degree in density	n (%)				0.339
	1	amorphous	9 (13.2)	9 (16.4)	
	2	intermediate	36 (53.0)	34 (61.8)	
	3	high	23 (33.8)	12 (21.8)	
Heterogeneity of density	n (%)				0.565
	1	homogeneous	48 (70.6)	39 (70.9)	
	2	heterogeneous	20 (29.4)	16 (29.1)	
Number	n (%)				0.397
	1	<20	25 (36.8)	14 (25.5)	
	2	20–35	21 (30.9)	19 (34.5)	
	3	>36	22 (32.4)	22 (40)	
Heterogeneity of size	n (%)				0.506
	1	homogeneous	27 (39.7)	21 (38.2)	
	2	heterogeneous	41 (60.3)	34 (61.8)	
Distribution area size	n (%)				0.009
(long axis × short axis mm^2)	1	<18	21 (30.9)	8 (14.5)	
	2	18–31	22 (32.3)	10 (18.2)	
	3	32–55	13 (19.1)	17 (30.9)	
	4	≥56	12 (17.7)	20 (36.4)	

SD: standard deviation

Table 2 Diagnostic factors of calcifications in breast cancer using multivariate logistic regression analysis

Characteristics of calcification		Odds ratio	95%CI	p Value
Distribution Area size (mm^2)				
	<18	1 (Reference)		<0.019
	18–31	1.30	0.41–4.18	0.657
	32–55	4.22	1.22–14.62	0.023
	≥56	5.55	1.50–20.62	0.01
Number		0.99	0.97–1.02	0.473
Heterogeneity of size		0.72	0.31–1.68	0.451
Heterogeneity of density		1.25	0.50–3.12	0.631
Degree in density		0.82	0.45–1.51	0.524

CI: confidence interval

heterogeneity of size (homogeneous, heterogeneous), and measurement of the distribution area size (DAS) of calcifications in the mediolateral oblique (MLO) view (multiplication of the greatest length by the width of the total zone of clustered calcifications in mm^2: less than 18, 18–31, 32–55, greater than 56) by quartile divisions.

These findings were correlated with pathological findings, and calcifications were classified as benign or malignant[11].

Pleomorphic clustered calcifications were classified into 2 categories by size, based on the criteria of BI-RADS 4th edition. Calcifications equal to or greater than 0.5 mm were defined as coarse heterogeneous calcifications those measuring less than 0.5 mm were classified as fine pleomorphic calcifications. These findings were correlated with pathological findings.

Statistical Analysis

We applied the chi-square test for bivariate comparisons and Student's *t*-test to compare the means of continuous variables. We used multivariate logistic regression analysis to evaluate aspects of calcifications as diagnostic factors in breast cancer.

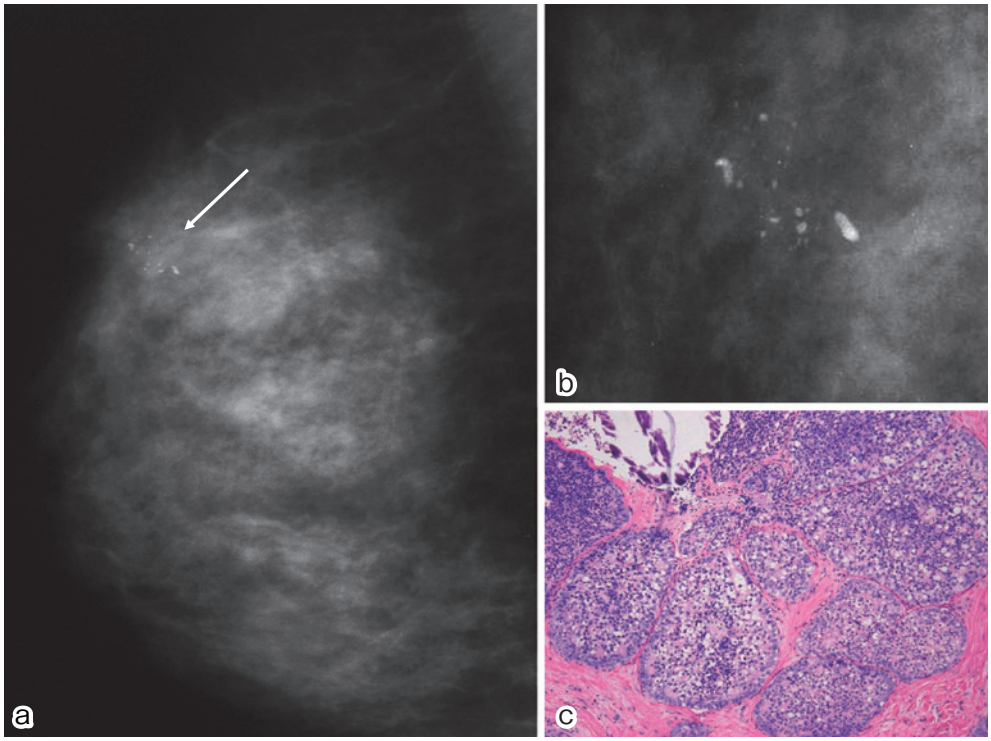

Fig. 1 A 42-year-old woman with a cluster of coarse heterogeneous calcifications on mammography.
a: Medio lateral oblique mammography revealed conspicuous clustered calcifications larger than 0.5 mm in upper part of the right breast (**arrow**). These calcifications are defined as coarse heterogeneous calcifications and are suggested to be benign lesions according to BI-RADS, 4th edition.
b: The distribution area size of the calcifications is 66 mm^2, and the possibility of malignancy was considered.
c: Pathologic examination revealed invasive ductal carcinoma with intraductal components (hematoxylin-eosin stain; original magnification, ×10).

The results of evaluations by the most effective characteristics and the BI-RADS 4th edition, criteria were compared using sensitivity, specificity, and area under the curve (AUC) for the receiver operating characteristic (ROC) curve.

When then analyzed the data using SPSS, 20. OJ (Should this be "IBM SPSS Statistics 20") (IBM Japan Ltd., Tokyo, Japan). Differences were considered significant when $p<0.05$.

Results

All patients were women aged 34 to 79 years (mean age: 50 years; SD: 10 years).

Pathological diagnoses were malignant lesions in 55 of 123 (44.7%) patients (48 non-invasive carcinoma, 5 invasive carcinoma, 2 ductal carcinoma), and benign lesions in 68 of 123 (55.3%) patients (13 fibroadenomas, 7 fibroadenomatosis, 4 mucocele-like tumors, 23 mastopathies, 1 hemangioma, 14 others, and 6 atypical intraductal lesions that were grouped with benign lesions)[11].

Relationship between 5 Calcification Characteristics and Status as Benign or Malignant

Table 1 shows the results of classifying calcifications on the basis of 5 characteristics (an atypical case was grouped with benign cases). The chi-square test showed significant differences in whether a calcification was malignant or benign only in terms of the DAS of calcification ($p=0.009$).

Results of multivariate logistic regression analysis where the DAS was classified into 4 categories are shown in **Table 2**. A DAS of 32 mm^2 or larger had a different association with malignancy than did a DAS smaller than 18 mm^2. There were significant

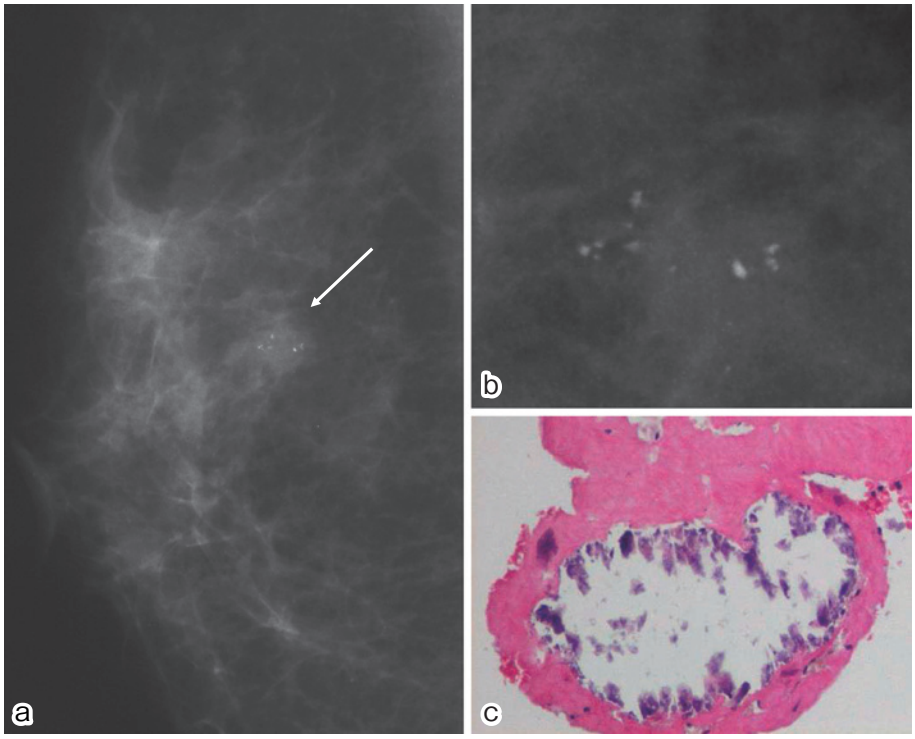

Fig. 2 A 55-year-old woman with a cluster of fine pleomorphic calcifications on mammography.
a: Medio lateral oblique mammography revealed clustered amorphous calcifications in the upper medial quadrant of the right breast **(arrow)**. These calcifications are defined as fine pleomorphic calcifications according to BI-RADS, 4th edition, and suggest malignancy.
b: The distribution area size of the calcifications is 21 mm^2, and the possibility of benign calcifications was considered.
c: Pathologic examination revealed calcified fibroadenoma (hematoxylin-eosin stain; original magnification, ×20).

differences in the association with malignancy of a DAS of 32-to 55 mm^2 (p=0.023, odds ratio=4.22) and more likely with a DAS of 56 mm^2 or larger (p=0.01, odds ratio=5.55), **(Fig. 1a–c)** than with a DAS smaller than 18 mm^2 **(Fig. 3a–c)** as a reference. There were no significant differences in the association with malignancy of a DAS of 18 to 31 mm^2 (p=0.657) **(Fig. 2a–c)** and a DAS smaller than 18 mm^2 **(Fig. 3a–c)**. However, malignancy tended to be less prevalent with a smaller DAS.

We classified calcifications by BI-RADS, 4th edition, criteria into 70 coarse heterogeneous calcifications cases, which included 39 benign and 31 malignant lesions according to pathological diagnosis, and 53 fine pleomorphic calcifications cases, which included 29 benign and 24 malignant lesions according to pathological diagnosis.

We compared the results of evaluations on the bases of DAS and BI-RADS 4th edition, criteria. This demonstrated significantly elevated AUC for ROC (AUC=0.67, 95% confidence interval [CI]=0.57–0.76, p=0.002) above evaluations based on the criteria of BI-RADS, 4th edition (AUC=0.51, 95% CI=0.40–0.61, p=0.925) **(Fig. 4)**.

Using a DAS of 18 mm^2 as the cut-off value resulted in a sensitivity of 85.5% and a specificity of 30.9%, whereas a DAS of 31 mm^2 resulted in a sensitivity of 67.3% and a specificity of 63.2%. A DAS of 56 mm^2 resulted in a sensitivity of 36.4% and a specificity of 82.4%. The BI-RADS, 4th edition, resulted in a sensitivity of 43.6% and a specificity of 82.4%.

Discussion

The BI-RADS, 4th edition, refined the classification

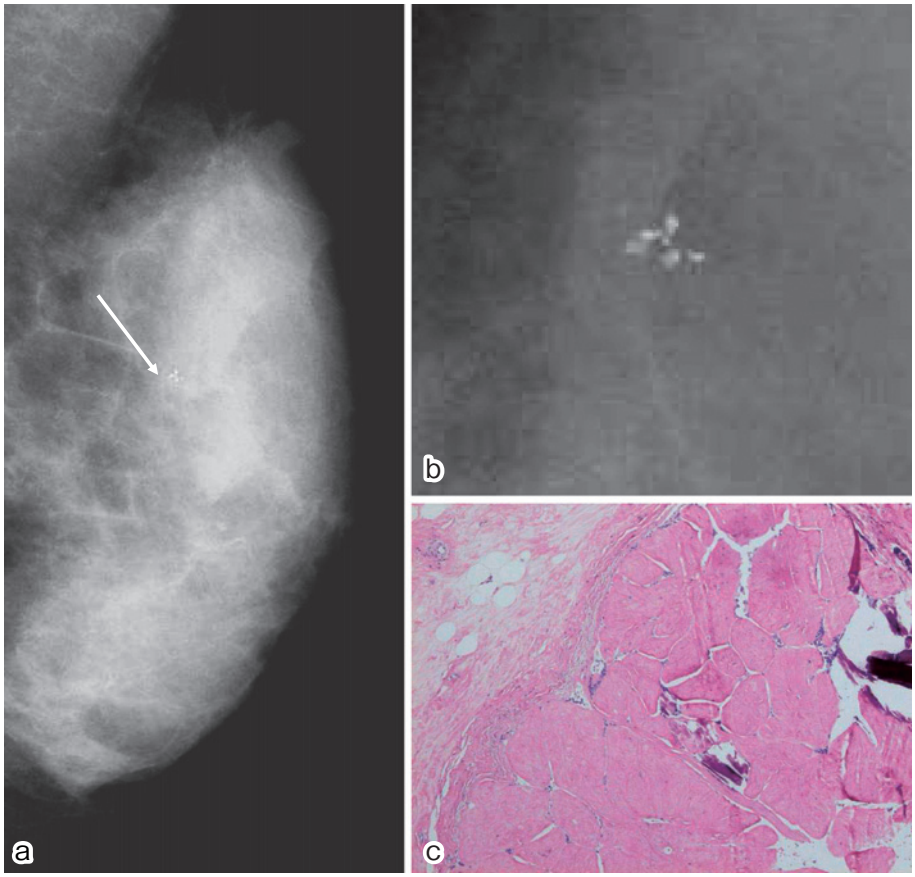

Fig. 3 A 38-year-old woman with cluster of coarse heterogeneous microcalcifications on mammography.
a: Medio lateral oblique mammography revealed clustered coarse heterogeneous calcifications in the upper part of the left breast **(arrow)**. These calcifications are defined as coarse heterogeneous calcifications suggesting benign lesions according to BI-RADS, 4th edition.
b[19]: The distribution area size of the calcifications was 6 mm^2, and the possibility of a benign lesion was considered.
c[19]: Pathologic findings revealed an old fibroadenoma (hematoxylin-eosin stain; original magnification, ×4).

of pleomorphic calcifications into 2 categories: coarse heterogeneous and fine pleomorphic[10]. A subsequent study showed a 7% (1 of 14) malignancy rate for coarse heterogeneous clustered calcifications and a 22% (6 of 27) rate for fine pleomorphic clustered calcifications[12]. Thus, these classifications improve risk classification. However, we have also observed many cases in which pleomorphic calcifications of nearly the same size and shape proved to be benign or malignant following stereotactically-guided VAB. Bent et al.[13] have reported a 25% (2 of 8) malignancy rate for coarse heterogeneous clustered calcifications and a 26% (9 of 34) malignancy rate for fine pleomorphic clustered calcifications. These results show the difficulty of differentiating between benign and malignant lesions on the basis of this classification alone. Further data on individually clustered pleomorphic calcifications are needed, as is indicated in the Guidance Chapter of the BI-RADS, 4th edition[10].

Variables, such as morphology and variations in size, density, and shading, previously used to make classifications, tend to be highly subjective[14–17].

However, Kettritz et al.[18] have reported that microcalcification morphology do not reliably predict malignancy. Our study also found that, these variables were not significant diagnostic factors for malignancy. The reason is that the calcifications we

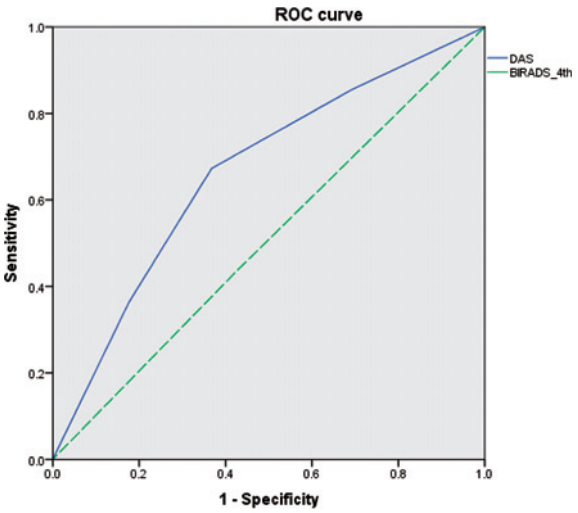

Fig. 4 ROC curves for the diagnosis of breast cancer with both DAS (AUC=0.67, 95% CI=0.57–0.76, p=0.002) and BI-RADS, 4th edition, criteria (AUC=0.51, 95% CI=0.40–0.61, p=0.925)
DAS: distribution area size;
ROC: receiver operating characteristic;
AUC: area under the curve

studied were limited to pleomorphic clustered calcifications. The extent area of calcifications, the so-called distribution, has been reported to be an important factor in diagnosing malignancy, with segmental distribution, more so than cluster distribution, being associated with a higher degree of malignancy[3,13,15].

Thus, in the present study, because we considered the extent area of calcifications to be important, even when limited to pleomorphic clustered calcifications, we examined the DAS.

Regarding the area of the cluster zone in square centimeters, De Lafontan et al.[15] have reported that the mean surface area of a cluster of microcalcifications was 1.35 cm^2 for benign disease and 2.26 cm^2 for malignant disease; however, the calcifications examined were of various morphologies and distributions. Our study is, to the best of our knowledge, the first to examine the DAS of pleomorphic clustered calcifications alone.

We found that of the 5 calcification characteristics, the DAS is the most significant index (**Table 1**). There was no correlation between the DAS and the number of calcifications, because the colleration coefficient was low (0.48).

The DAS of clustered calcifications is a quantitative value and free of interpretive differences. In addition, the recent full-field digital mammography reading with monitor makes area measurements even easier. The DAS is a useful variable, because in cases in which calcifications are dense, exceeding 0.5 mm in size (**Fig. 1a–c**), and would be classified as coarse heterogeneous calcifications by BI-RADS, 4th edition, criteria, a DAS greater than 32 mm^2 suggests the calcification is likely to be malignant. Such cases merit further investigation via stereotactically-guided VAB. Even in cases in which calcifications are indistinct, measure 0.5 mm in size (**Fig. 2a–c**), and would be classified as fine pleomorphic calcifications by BI-RADS 4th edition criteria, the current results suggest that a DAS of less than 31 mm^2 merits examination of the possibility that the calcification is benign. Based on the results in **Table 2**, benignity tended to be more likely with a smaller DAS as in **Figure 3a–b**. Nevertheless, there is a 27.6% probability of malignancy even with a DAS smaller than 18 mm^2.

Further examination via a stereotactically-guided VAB should be performed if a DAS is 32 mm^2 or larger (greater probability of malignancy in about 60%). About 30% of calcifications are malignant if they have a DAS of 31 mm^2 or smaller, so DAS alone cannot be used to determine whether a biopsy is indicated. The DAS resulting in an AUC of 0.67 is not a certain value. Thus, DAS is useful for determining whether a calcification is benign or malignant, but classification based on DAS alone is impractical. The DAS must be considered in conjunction with other factors. Thus, DAS is useful for determining whether a calcification is benign or malignant, but classification based on DAS alone is impractical. The DAS must be considered in conjunction with other factors.

A limitation of this study is that the DAS refers to the area measured from an MLO view, not volume. Based on an emphasis on simply and ease of clinical application, this study compared the area of calcifications from an MLO view. However, precise mesurements of the DAS of calcifications are ideally done in three dimentions based on comparisons of

volume, (i.e., also using the depth in the cranio-caudal view).

In conclusion, the diagnostic accuracy of DAS is significant in making diagnoses and in determining differentiating whether clustered pleomorphic calcifications are benign or malignant. The use of the DAS is a new, reliable, and simple method that can easily be integrated into routine practice. The DAS improves diagnostic acuuracy and is useful for determining whether to proceed with biopsies.

Conflict of Interest: The authors have no conflicts of interest to declare.

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