


The predictive value of calcification for the grading of ductal carcinoma in situ in Chinese patients

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Abstract

High-grade ductal carcinoma in situ (DCIS) requires resection due to the high risk of developing invasive breast cancer. The predictive powers of noninvasive predictors for high-grade DCIS remain contradictory. This study aimed to explore the predictive value of calcification for high-grade DCIS in Chinese patients.

This was a retrospective study of Chinese DCIS patients recruited from the Women's Hospital, School of Medicine, Zhejiang University between January and December 2018. The patients were divided into calcification and non-calcification groups based on the mammography results. The correlation of calcification with the pathologic stage of DCIS was evaluated using the multivariable analysis. The predictive value of calcification for DCIS grading was examined using the receiver operating characteristics (ROC) curve.

The pathologic grade of DCIS was not associated with calcification morphology ($P = .902$), calcification distribution ($P = .252$), or breast density ($P = .188$). The multivariable analysis showed that the presence of calcification was independently associated with high pathologic grade of DCIS (OR=3.206, 95% CI=1.315–7.817, $P = .010$), whereas the age, hypertension, menopause, and mammography BI-RADS were not (all $P > .05$) associated with the grade of DCIS. The ROC analysis of the predictive value of calcification for DCIS grading showed that the area under the curve was 0.626 ($P = .019$), with a sensitivity of 73.1%, specificity of 52.2%, positive predictive value of 72.2%, and negative predictive value of 53.3%.

The presence of calcification is independently associated with high pathologic grade of DCIS and could predict high-grade DCIS in Chinese patients.

Abbreviations: BI-RADS = breast imaging reporting and data system, DCIS = ductal carcinoma in situ, ROC = receiver operating characteristics.

Keywords: breast cancer, calcification, ductal carcinoma in situ, tumor grade

1. Introduction

Ductal carcinoma in situ (DCIS) of the breast is a spectrum of malignant cells within the breast ducts without invading the ducts or surrounding tissues.^[1] The incidence of DCIS is 32.5 per 100,000 women^[1] and peaks at 96.7 per 100,000 women aged 65 to 69 years.^[1] The increased incidence of DCIS in the last decade is directly associated with the implementation of screening

programs worldwide.^[1] DCIS is considered a precursor lesion to invasive breast cancer.^[2] The general risk factors for DCIS are the same as for invasive breast cancer, including older age, Caucasian race, later age at first birth, lower number of children, increased breast density, and a family history of breast cancer.^[1] Since breast biopsy only takes a small part of the total lesion, resection of biopsy-proven DCIS is required to ensure the absence of invasive foci.^[3–5]

Mammography and breast ultrasound can identify typical breast cancer-associated abnormalities, including calcifications, masses, distortions, and asymmetries.^[6,7] However, these abnormalities also occur in benign or pre-malignant breast diseases,^[8–10] which makes it difficult for the radiologists and physicians to decide about appropriate patient management, such as additional imaging, biopsy, and surgery. The Breast Imaging Reporting and Data System (BI-RADS) classifies the lesions into risk categories for breast cancer^[6]; however, this system cannot distinguish DCIS from invasive breast cancer or low-grade DCIS from high-grade DCIS. Because high-grade DCIS has a significantly higher risk of developing invasive breast cancer than low-grade DCIS and requires early surgery,^[11,12] it is critical to identify a reliable predictor for high-grade DCIS.

Previous studies have examined the association of different types of calcification with high-grade DCIS^[13–16]; however, these studies were limited by the subjective designation of the calcification type and the restricted mammographic views. Since 80% to 90% of DCIS lesions are calcified,^[17,18] and high-grade

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DCIS may be uncalcified,^[15] we wondered whether the presence of calcification could predict high-grade DCIS.

In this study, we explored the predictive value of calcification for the grading of DCIS. Our results may provide helpful information for the management of patients with DCIS.

2. Patients and methods

2.1. Study design and subjects

This retrospective study recruited 124 patients with biopsy-confirmed DCIS with or without calcification at the Women's Hospital, School of Medicine, Zhejiang University (Hangzhou, Zhejiang, China) between January and December 2018. The study was approved by the ethics committee of the Women's Hospital, School of Medicine, Zhejiang University (20190061). The informed consent was waived because this study was retrospective.

The inclusion criteria were:

- 1) patients needed further examinations due to a clinical diagnostic requirement or abnormal breast screening;
- 2) pathologically confirmed DCIS; and
- 3) complete clinical information, such as the breast X-ray and ultrasound images.

The exclusion criteria were:

- 1) pregnancy;
- 2) breast implants;
- 3) breast X-ray and ultrasound images failing to meet the requirements for diagnosis; or
- 4) vital organ dysfunctions or mental disorders preventing the patients from undergoing the routine management for breast lesions.

2.2. Grouping

The patients were divided into calcification and non-calcification groups based on the breast mammography results.

2.3. Examinations

Full-field digital mammography was performed using a Selenia Dimensions digital breast X-ray imaging system (Hologic, Inc., Bedford, MA). During the examination, the patient was in a standing position, and the upper body was completely exposed. All metals on the body surface were removed, and the breast tissue was fully pressed against the detector. The Auto-Filter mode was selected to take the craniocaudal and mediolateral oblique images of both breasts. The mammographic X-ray images were analyzed according to the BI-RADS, including the distribution, size, morphology, margins, and density of the lesion, the presence, morphology, and distribution of calcification, skin and nipple conditions, as well as the presence of swollen axillary lymph nodes. Partially enlarged images of the lesion were acquired if necessary. Breast density was quantified based on the mammographic X-ray images.

Breast ultrasound was conducted using the LOGIQ E9 and Voluson E8 color Doppler ultrasound systems and a linear array 6- to 15-MHz probe (GE Healthcare, Waukesha, WI). During the examination, the patient was in a supine position, and both sides of the breast and armpit were fully exposed. A radial scan of the

breast, with the nipple as the center, was performed, including the four quadrants, the nipple-areola area, axillary tail, and armpit area. The lesion size, position, internal echoes, aspect ratio, boundary, margin, morphology, envelope, calcification, the presence or absence of attenuation in the back, and the relationship between the mass and surrounding tissues were recorded. The blood flow inside and around the lesion was examined by color Doppler flow imaging.

2.4. Data collection

Variables, including age, hypertension, family history of breast cancer, menopause, and pathological results, were collected from the electronic medical record.

2.5. Statistical analysis

The continuous data that followed normal distribution were presented as the mean \pm standard deviation and tested using the independent sample *t* test. The data that did not follow the normal distribution were presented as the medians (interquartile range) and tested using the Mann-Whitney *U* test. The categorical data were described using numbers and percentages and tested using the chi-square test or Fisher exact test. The grading data were tested using the Mann-Whitney *U* test. Potential confounding variables were subjected to a multivariable logistic regression analysis to determine their associations with high-grade DCIS. The predictive value of calcification for DCIS grading was examined using the receiver operating characteristics (ROC) curve. SPSS 22.0 (IBM, Armonk, NY) was used for statistical analysis. A *P* value $< .05$ was considered statistically significant.

3. Results

3.1. Characteristics of the patients

A total of 124 Chinese women with DCIS were enrolled in this study, including 79 patients with calcification and 45 patients without calcification. The characteristics of the patients were summarized in Table 1. No significant differences were observed in the age, family history of breast cancer, menopause, staging by infiltration, and surgical approach between the two groups (all $P > .05$). Compared with the non-calcification group, the calcification group had a lower percentage of hypertension (7.6% vs 22.2%, $P = .019$), more advanced BI-RADS stage by mammography ($P < .001$) and breast ultrasound ($P = .024$), higher pathologic grade (high grade: 72.2% vs 46.7%, $P < .001$), and a higher percentage of invasive foci (65.8% vs 46.7%, $P = .037$). These data indicate that the calcification group has more aggressive features than the non-calcification group.

3.2. The mammographic features of calcification are not associated with the pathologic stage of DCIS

It has been reported that mammographic features of calcification, such as linear distribution and coarse heterogeneity, are correlated with high-grade DCIS.^[14] However, we did not observe significant differences in the calcification morphology ($P = .902$), calcification distribution ($P = .252$), and breast density ($P = .188$) between the patients with low/medium- and high-stage DCIS (Table 2), suggesting that the mammographic features of

Table 1
Characteristics of the patients.

Variables	Calcification (n=79)	No calcification (n=45)	P
Age (yr)	48 (40–57)	48 (44–56)	.171
Hypertension	6 (7.6%)	10 (22.2%)	.019
Family history of breast cancer	0	2 (4.4%)	.130
Menopause	27 (34.2%)	18 (40.0%)	.517
Mammography BI-RADS			<.001
2	1 (1.3%)	4 (8.9%)	
3	12 (15.2%)	22 (48.9%)	
4	51 (64.6%)	17 (37.8%)	
5	13 (16.5%)	2 (4.4%)	
6	2 (2.5%)	0	
Ultrasound BI-RADS			.024
0	1 (1.3%)	0	
3	7 (8.9%)	10 (22.2%)	
4	55 (69.6%)	31 (68.9%)	
5	14 (17.7%)	4 (8.9%)	
6	2 (2.5%)	0	
Pathological staging			<.001
Low	7 (8.9%)	20 (44.4%)	
Medium	15 (19.0%)	4 (8.9%)	
High	57 (72.2%)	21 (46.7%)	
With infiltration	52 (65.8%)	21 (46.7%)	.037
Staging by infiltration			.535
I	6 (11.5%)	4 (19.1%)	
II	21 (40.4%)	8 (38.1%)	
III	25 (48.1%)	9 (42.9%)	
Surgery			.303
Breast-conserving surgery	19 (24.7%)	15 (33.3%)	
Mastectomy	58 (75.3%)	30 (66.7%)	

calcification are not associated with the pathologic stage of DCIS at least in Chinese patients.

3.3. The presence of calcification is independently correlated with the pathologic stage of DCIS

Then, we performed a multivariable analysis to examine the correlations of calcification and other clinical variables with the pathologic stage of DCIS. As shown in Table 3, only the presence

of calcification was independently associated with high pathologic grade of DCIS (odds ratio=3.206, 95% confidence interval=1.315–7.817, $P=.010$), whereas age, hypertension, menopause, and mammography BI-RADS were not associated with the grade of DCIS (all $P>.05$). These data suggest that the presence of calcification might provide additional information regarding the stage of DCIS in Chinese patients. This finding is consistent with previous studies^[19–21] showing that the appearance of microcalcifications on ultrasound is associated with high-grade DCIS.

3.4. The presence of calcification predicts high-stage pathology of DCIS.

To examine the predictive value of calcification for the staging of DCIS, we performed the ROC curve analysis. As shown in Figure 1, the area under the curve was 0.626 ($P=.019$), with a sensitivity of 73.1%, specificity of 52.2%, positive predictive value of 72.2%, and negative predictive value of 53.3%. This finding suggests that the presence of calcification could predict high-stage pathology of DCIS in Chinese patients, providing valuable information for the physicians to make treatment decisions.

4. Discussion

High-grade DCIS requires early resection due to the high risk of developing invasive foci. Predictors for high-grade DCIS remain contradictory. This study aimed to explore the predictive value of calcification for the grading of DCIS. Our results suggest that the presence of calcification is independently associated with high pathologic grade of DCIS, whereas the type and distribution of calcification are not associated with the pathologic grade of DCIS.

Yamada et al^[16] have reported that low-grade DCIS without necrosis is less likely to display calcifications than high-grade DCIS or DCIS with necrosis. On the other hand, Hayward et al^[15] have shown that high-grade DCIS could be uncalcified. In the present study, 36% of patients with DCIS, regardless of grade, did not show calcification. High-grade DCIS occurred in 47% of patients without calcification and 66% patients with calcification. The multivariable analysis showed that calcification

Table 2
Morphology and distribution of the calcifications in the calcification group.

Indicators	Total (n=79)	Pathological staging: low + medium (n=22)	Pathological staging: high (n=57)	P
Calcification morphology				.902
Amorphous	19 (24.1%)	6 (27.3%)	13 (22.8%)	
Coarse heterogeneous	14 (17.7%)	4 (18.2%)	10 (17.5%)	
Fine pleomorphic	46 (58.2%)	12 (54.5%)	34 (59.6%)	
Fine linear or fine linear branching	0	0	0	
Calcification distribution				.252
Diffuse	15 (19.0%)	6 (27.3%)	9 (15.8%)	
Regional	5 (6.3%)	0	5 (8.8%)	
Grouped	38 (48.1%)	13 (59.1%)	25 (43.9%)	
Linear	2 (2.5%)	0	2 (3.5%)	
Segmental	19 (24.1%)	3 (13.6%)	16 (28.1%)	
Breast density				.188
b	7 (8.9%)	3 (13.6%)	4 (7.0%)	
c	69 (87.3%)	17 (77.3%)	52 (91.2%)	
d	3 (3.8%)	2 (9.1%)	1 (1.8%)	

Table 3
Multivariable analysis of pathological staging.

Variables	Univariable			Multivariable		
	OR	95%CI	P	OR	95%CI	P
Calcification	2.960	(1.378–6.361)	.005	3.206	(1.315–7.817)	.010
Age	0.987	(0.954–1.021)	.458	1.026	(0.962–1.094)	.435
Hypertension	0.727	(0.251–2.104)	.556	1.254	(0.348–4.521)	.730
Menopause	0.613	(0.289–1.301)	.203	0.373	(0.097–1.428)	.150
Mammography BI-RADS						
2	0.767	(0.120–4.917)	.779	1.559	(0.211–11.514)	.664
3	0.575	(0.248–1.332)	.197	0.858	(0.331–2.225)	.753
4	Reference			Reference		
5	1.405	(0.403–4.903)	.594	1.274	(0.342–4.741)	.718
6	0.511	(0.031–8.549)	.641	0.444	(0.023–8.741)	.594

CI=confidence interval, OR=odds ratio.

was independently associated with high-grade DCIS. The ROC curve analysis showed that calcification could predict high-grade DCIS, but the sensitivity (73%) and specificity (52%) were relatively low. Therefore, a predictive model incorporating multiple variables, including calcification, should be established in future studies.

Our results provide important information for clinical practicing because high-grade DCIS is associated with a higher likelihood of the presence of invasive foci and that the presence of invasive foci could change the prognosis and management of the patient.^[3,22] Previous studies have attempted to identify the factors associated with DCIS grade or with the rate of upgraded diagnosis of invasive carcinoma from final surgical pathologic findings, but the results remain inconsistent.^[5,23–34] Han et al^[26] have reported that calcification, palpable mass, and solid DCIS

are associated with more advanced DCIS. Park et al^[20] have reported that calcifications with ductal changes are associated with high-grade DCIS. These findings are consistent with our results. On the other hand, some studies have shown that other imaging lesions are associated with more advanced DCIS.^[34–38] Contrary to our findings, Isozaki et al^[39] have reported that the absence of calcification is associated with the presence of invasive foci at surgery. These contradictory results may be related to the differences in patient race, radiologists' experience, sample size, screening/diagnostic imaging approach, local practice, and DCIS management.

Previous studies have examined the association of different types of calcification with high-grade DCIS,^[13–16] but these studies may be limited by the subjective designation of calcification types and the restricted views of mammography. Zunzunegui et al^[13] have shown that the casting-like calcification is associated with invasive disease in patients with DCIS. Rauch et al^[14] have demonstrated that fine linear branching calcification is associated with DCIS recurrence, dense breasts, and lesion size. Unlike the findings of these studies, we did not observe any association of calcification morphology, calcification distribution, or breast density with the pathologic stage of DCIS. The discrepancy might be due to the sample size, the radiologist's subjective designation of the calcification type, or the quality of mammogram images. For example, breast positioning might affect the radiologist's judgment of linear calcification.

This study has limitations. It was a retrospective study using a relatively small sample size. The patients were from a single center in a short period of time. Only the data from the medical record were available for analysis. No follow-up was performed. Further research is necessary to determine the predictors of DCIS grade.

In conclusion, our results suggest that the presence of calcification is independently associated with high pathologic grade of DCIS, whereas the type and distribution of calcification are not associated with the pathological grade of DCIS. This finding may provide valuable information for treatment options for DCIS in clinical practicing.

Author contributions

KJ and ZY carried out the studies, collected the data, participated in statistical design and analysis, and drafted the manuscript. ZX participated in statistical design and analysis. LX participated in

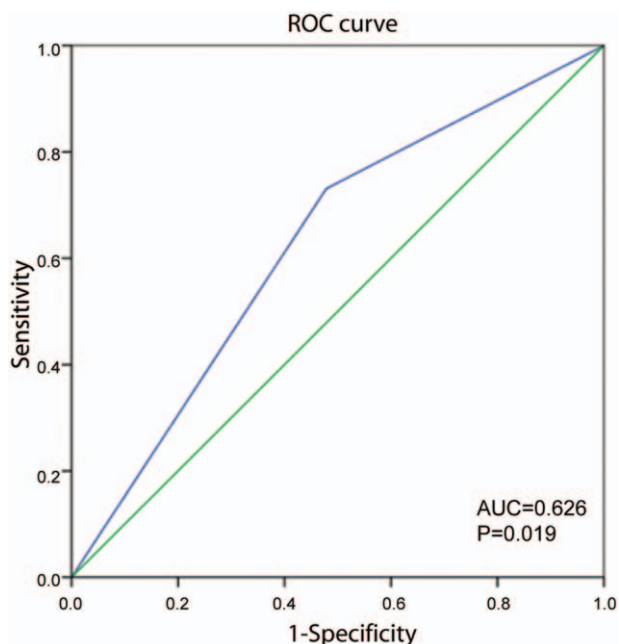


Figure 1. Receiver operating characteristics curve analysis of calcification in predicting the grade of ductal carcinoma in situ. The area under the curve was 0.626 ($P=.019$), with a sensitivity of 73.1%, specificity of 52.2%, positive predictive value of 72.2%, and negative predictive value of 53.3%. ROC = receiver operating characteristics, AUC = area under the curve.

data collection, analysis, and interpretation and drafted the manuscript. All authors read and approved the final manuscript.

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