Mammographic Features Are Associated with Clinicopathological Characteristics in Invasive Breast Cancer

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Abstract. *Aim: To assess the correlation between mammographic features and clinicopathologic characteristics of invasive breast carcinoma. Patients and Methods: The mammographic appearance and clinicopathological data of 108 invasive ductal carcinomas were retrospective analyzed. The mammographic features were assessed according to BI-RADS by two doctors. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2) and Ki-67 were analyzed on the surgically removed tumor samples by immunohistochemical staining analysis. The clinical information, including age, menopausal status, tumor size, grade, stage, and axillary lymph node status, were collected from our database. Statistical analysis was performed to assess the correlation between mammographic features and clinicopathologic characteristics. Results: Based on pathologic analysis, 19 out of the 108 (18%) patients had invasive ductal carcinoma (IDC) accompanied by component of ductal carcinoma in situ (DCIS); another 89 cases (82%) were pure IDC. Sixty-three patients had a mass on the mammogram; the mammographically visible mass was frequently observed in histologically pure IDC, while mammographic calcification was significantly associated with IDC accompanied with DCIS ($p<0.01$). Mammographic calcification accompanied by evident mass was correlated with axillary lymph node metastasis ($p<0.05$). The tumor size was usually larger than 2 cm when the mammographic mass was accompanied by calcification ($p<0.01$). Tumors from patients presenting with spiculated mass had a significantly higher ER-positive and PR-positive rates than those from patients presenting with non-spiculated mass (92.59% vs. 63.89%, $p<0.01$, and 92.59% vs. 44.44%, $p<0.01$, respectively). Tumors from patients presenting with spiculated mass had Her2 negativity ($p<0.05$) and lower proliferative activity as labeled by Ki-67 compared with those from patients presenting with non-spiculated mass ($p<0.01$). Conclusion: Based on our current findings, the mammographic appearance reflects the biologic behavior of the breast tumor and should be taken into account when planning treatment for IDC.*

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Worldwide, it is estimated that more than one million women are diagnosed with breast cancer every year, and it accounts for about 410,000 deaths per year (1). Breast cancer is already the leading cause of cancer in Southeast Asian women, and is second only to gastric cancer in East Asian women (2). In some areas of China, the incidence of breast cancer was recorded to be increasing by 5% per year, an increase greater than that worldwide (3). The application of mammography benefits more and more patients by leading to earlier detection and management because the introduction of mammography screening has led to an increased detection of smaller invasive tumors without local or distant metastasis.

Breast cancer often exhibits intratumoral heterogeneity, so that mammographic patterns of breast cancer have a wide range of variation. Recently, we reported that mammographically occult breast cancer had a worse prognosis compared with

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mammographically positive breast cancer (4). In addition, it has been reported that some particular histological types of breast carcinomas have certain specific mammographic features. Mucinous carcinoma of the breast usually presents as a mass with a well-defined margin rather than a spiculated one, and is associated with the absence of calcifications (5-7), while tubular carcinoma of the breast usually manifests as a small spiculated mass (8-10). Both of these types have more favorable prognosis than common invasive ductal carcinoma. To our knowledge, there are few articles reporting the mammographic features of invasive ductal carcinomas (IDC).

The aim of the current study was to evaluate the different types of mammographic tumoral appearances for their relationships with clinical, pathological and biological characteristics in a series of patients with IDC.

Patients and Methods

Patients. Patients involved in this study were a series of 108 cases who underwent surgery in Qilu Hospital Shandong University between June 2008 and March 2010. All cases were of unilateral breast ductal carcinoma and all patients were women between the ages of 27 and 79 years (mean age 49 years). Sixty-two out of 108 women were premenopausal, 46 were postmenopausal. All patients received preoperative mammography bilaterally without regard to whether the lesion was palpable. Clinical information, mammograms and pathological data of each patient for the duration of hospital stay were collected.

Mammography. Every patient received mammography screening bilaterally before the surgery with the use of a Mammomat Novation DR system (Simmens AG, Germany). Craniocaudal view (CC) and mediolateral view (ML) were performed routinely for all patients, and mediolateral oblique view (MLO) was obtained when necessary. All mammograms were reviewed by two skilled doctors blinded to the pathological and clinical information. All the mammograms were assessed according to the analytic criteria of Breast Imaging Reporting and Data System (BI-RADS) in which the mammographic features mass, calcification, architectural distortion and asymmetric density were recorded (11).

In this study, patients with a mass on the mammogram were divided into groups of spiculated and non-spiculated or regular and irregular, according to the shape or margin of the mass, respectively. The density of mammogram was classed into four groups: I: the breast is almost entirely fat (<25% glandular); II: there are scattered fibroglandular densities (approximately 25-50% glandular); III: the breast tissue is heterogeneously dense (approximately 51-75% glandular); IV: the breast tissue is extremely dense (>75% glandular). The morphology and distribution of calcification was not taken into account because the number of the patients with calcification was too low for statistical analysis.

Histopathology and immunohistostaining analysis. All the tumors were IDC, some of which were accompanied by component of ductal carcinoma *in situ* (DCIS), with infiltrative peculiar carcinomas excluded. In this study, histology category was classified into two groups, unmixed IDC and IDC with component of DCIS. The tumor size and grade of IDC were also taken into account. Grades of IDC were classified into three levels according to the Scarff-Bloom-Richardson system, the grade being determined by the frequency of cell mitosis, tubule formation (percentage of tumor composed of tubular structures), and nuclear pleomorphism (change in cell size and uniformity) (12). The axillary lymph node status was described as being positive or negative. The tumor stage was determined according to the American Joint Committee on Cancer Staging for Breast Cancer (13).

The immunohistostaining analysis was performed with PV-9000 Polymer Detection System for Immuno-Histological Staining (GBI, USA). The paraffin embedded tumor sections were deparaffinized and gradually rehydrated through changes of graded ethanol from 100% to distilled water. The sections were then incubated in 3% perhydrol for 10 minutes to block endogenous peroxidase. Pretreatment of sections was carried out with 0.1M Tris/HCl (pH6) for 15 minutes at 98˚C. Primary antibodies against estrogen recptor (ER) (clone 1D5), progesterone receptor (PR) (clone SP2), human epidermal growth factor receptor 2 (Her2) (clone CB11) and Ki-67 (clone K-2) (all GBI) were diluted and added to sections which were then incubated at 28˚C for 3 hours. Samples were then washed in three changes of phosphate-buffer saline (PBS) for 2 minutes each and sequentially incubated with Polymer Helper and poly peroxidase-anti-mouse/rabbit IgG at 37˚C for 20 minutes. The diaminobenzidine (DAB) reaction was used in order to visualize the complex of antibody-antigen. After a final wash with distilled water, counterstaining with hematoxylin, dehydrating through graded ethanol series and then mounted. Immunohistochemistry was successful in all 108 cases for ER, PR, Her2 and Ki-67 staining.

ER and PR were considered positive if nuclear staining was present in ≥10% of the cells, and Ki-67 expression was considered positive in cases of a substantial percentage of positively stained nuclei (>30%). Her2 expression was graded as recommended by the HercepTest™ scoring guidelines as: 0: no staining at all or membrane staining in <10% of tumor cells; 1+: a faint/barely perceptible partial membrane staining in >10% of the tumor cells; 2+: weak to moderate complete membrane staining in >10% of tumor cells; 3+: strong complete membrane staining in>10% of cells. Her2/neu was considered to be positive if the score was 2+ or 3+.

Statistical analysis. All data were analyzed using Statistical Package for the Social Sciences statistical software (version 10.0; SPSS Inc., Chicago, IL, USA). Correlations between mammographic appearance and clinicopathological parameters of IDC were also evaluated by chi-square test. All statistical tests were two-sided. A *p*-value of ≤0.05 was considered as being significant.

Results

As shown in Table I, the 108 patients involved in this study ranged in age from 27 to 79 years (mean 49 years). Fifty-seven percent (n=62) of the patients were premenopausal and 43% (n=46) were postmenopausal. As shown in Table II, 18% (n=19) of the tumors manifested mammographic low density and 82% high density. Fifty-eight percent (n=63) of the patients had a mammographic mass (Figure 1), 44% (n=48) had calcifications, 23% (n=25) had both a mass and calcifications on the mammogram (Figure 2), and 8% (n=9) had architectural distortion (Figure 3). In addition, 12% (n=13) of the tumors were invisible on mammography. In

Table I. *Clinicopathological characteristics of the patients.*

Age, years (mean, range)	49 (27-79)
Menopausal status (n=108)	
Premenopausal	62 (57.41%)
Postmenopausal	46 (42.59%)
Lymph node status (n=105)	
Negative	59 (56.19%)
Positive	46 (43.81%)
Menarche age, years (n=108)	
≤13	30 (27.78%)
>13	78 (72.22%)
Histology (n=108)	
Invasive ductal	89 (82.41%)
Invasive ductal with DCIS	19 (17.59%)
Tumor size, cm (n=102)	
≤2	55 (53.92%)
>2	47 (46.08%)
Grade of invasive ductal carcinoma(n=98)	
I	10 (10.20%)
II	74 (75.51%)
III	14 (14.29%)
Estrogen receptor-positive (n=108)	82 (75.93%)
Progesterone receptor-positive (n=108)	72 (66.67%)
Her2 -positive (n=108)	29 (26.85%)
Ki-67-positive (n=108)	61 (56.48%)
Triple negative (n=108)	15 (13.89%)

DCIS: Ductal carcinoma *in situ*.

Table II. *Mammographic features of breast tumors.*

Calcification*(n=108)	48 (44.44%)
Mass** (n=108)	63 (58.33%)
Margin (n=63)	
Spiculated	27 (42.86%)
Non-spiculated	36 (57.14%)
Shape (n=63)	
Regular	10 (15.87)
Irregular	53 (84.13%)
Negative (n=108)	13 (12.04%)
Calcification only (n=108)	23 (21.30%)
Mass only (n=108)	38 (35.18%)
Calcification with mass (n=108)	25 (23.15%)
Architectural distortion (n=108)	9 (8.33%)
Percentage density of breast	
Almost entirely fat (<25% glandular)	19 (17.59%)
Scattered fibroglandular densities (25-50%)	38 (35.19%)
Heterogeneously dense (51-74%)	31 (28.70%)
Extremely dense (>75%)	20 (18.52%)

*Including all cases that showed calcification on the mammogram.
**Including all cases that showed mass on the mammogram.

Table III. *Correlations between mammographic density and clinicopathologic features.*

	Low density	High density	*P*-value
Age (years)			
≤50	5	59	<0.01
>50	14	30	
Menarche age (years)			
≤13	3	27	>0.05
>13	16	62	
Menopausal status			
Premenopausal	3	59	<0.01
Postmenopausal	16	30	
Estrogen receptor status			
Negative	6	20	>0.05
Positive	13	69	
Progesterone receptor status			
Negative	8	28	>0.05
Positive	11	61	
Ki-67 status			
Negative	7	40	>0.05
Positive	12	49	

other words, there were 23 patients with calcifications only on the mammogram, and 38 patients with evident mass without calcifications on the mammogram. When a mass was visible in both CC and ML views, the margin and shape were assessed. Forty three percent (n=27) of the 63 tumors had a spiculated margin, and 16 % (n=10) were regular in shape. All 108 cases were demonstrated to have IDC pathologically. Eighty-two percent (n=89) were purely IDC, and 18% (n=19) were accompanied by components of DCIS. The tumors ranged in size from 0.5 cm to 9 cm. Histological grade was assessed in 98 patients according to the Scarff-Bloom-Richardson system. Ten percent (n=10) of the tumors were grade I, 76% (n=74) were grade II, and 14% (n=14) were grade III. Axillary lymph nodes were dissected for 105 patients, 44% (n=46) were found to be tumor positive. Immunohistochemical staining was performed on paraffin sections of all the 108 cases for ER, PR, Her2 and Ki67. Seventy-six percent (n=82) were positive for ER, 67% (n=72) for PR, 27% (n=29) for Her2, and 56% (n=61) for Ki-67. Furthermore, 14% (n=15) of the patients were triple negative for ER, PR and Her2.

High mammographic density was associated with young age (<50 years) and premenopausal status ($p<0.05$) (Table III). As shown in Table IV, postmenopausal patients usually showed a mass on the mammogram more frequently than premenopausal ones ($p<0.05$). The majority of masses were unmixed IDC ($p<0.01$), whereas the majority of calcifications were found in cases of those accompanied by component of DCIS ($p<0.01$). As shown in Table V, if the lesions appeared as calcification on the mammogram, whether with or without mass, the tumor was usually larger than 2 cm in size ($p<0.01$) and with axillary lymph node metastasis ($p<0.05$).

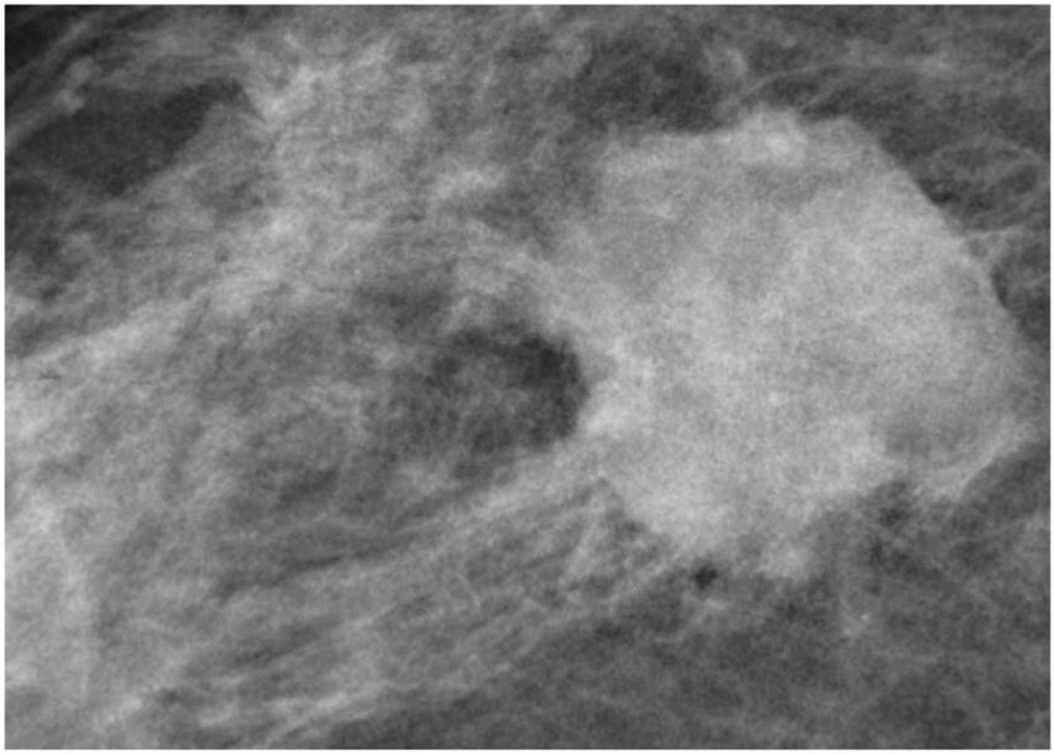

Figure 1. *Invasive ductal carcinoma presenting as mass on the mammogram.*

Table IV. *Correlation between breast mass and clinicopathologic parameters.*

Clinicopathologic parameter	Mass* n(%)		χ^2	*P*-value
	Negative	Positive		
Menopausal				
Premenopausal status	31 (28.70%)	31 (28.70%)	4.1590	0.0497
Postmenopausal	14 (12.96%)	32 (29.63%)		
Histology				
Invasive ductal	29 (26.85%)	60 (55.56%)	17.1694	<0.0001
Invasive ductal with DCIS	16 (14.81%)	3 (2.78%)		

*Corresponds to those cases presenting masses on the mammogram with or without calcifications. DCIS: Ductal carcinoma *in situ*.

Table V. *Correlation between tumor calcification and clinicopathologic parameters.*

Clinicopathologic parameter	Calcification* n(%)		χ^2	*P*-value
	Negative	Positive		
Histology				
Invasive ductal	55 (50.93%)	34 (31.48%)	7.9834	0.0096
Invasive ductal with DCIS	5 (4.63%)	14 (12.96%)		
Tumor size (cm)				
≤2 cm	40 (39.22%)	15 (14.71%)	13.7378	0.0003
>2 cm	17 (16.67%)	30 (29.41%)		
Node status				
Negative	39 (37.14%)	20 (19.05%)	6.4281	0.0172
Positive	19 (18.10%)	27 (25.71%)		

*Corresponds to those cases presenting calcification on the mammogram with or without an evident mass. DCIS: Ductal carcinoma *in situ*.

To further explore the correlation between mammographic features and clinicopathological characteristics, we divided the patients into 5 groups according to the mammographic appearance (Table VI): negative, type A calcification only, type B mass only, type C mass associated with calcification and, type D architectural distortion only. We did not find any significant relationship between architectural distortion and clinicopathologic parameters in our study. There was no significant difference in clinicopathologic characteristics between mammographically negative and positive types. Patients presenting with Type A tumors were more frequently to have IDC associated with DCIS in histopathology than other

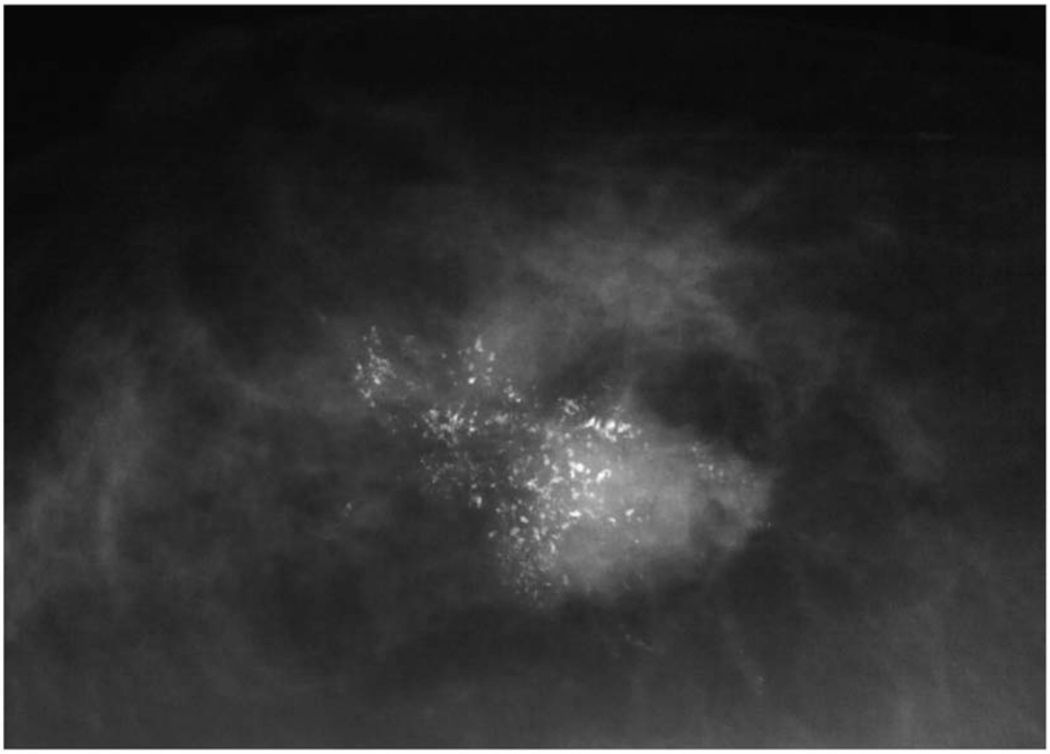

Figure 2. *Invasive ductal carcinoma accompanied by ductal carcinoma in situ presenting as mass with calcification on the mammogram.*

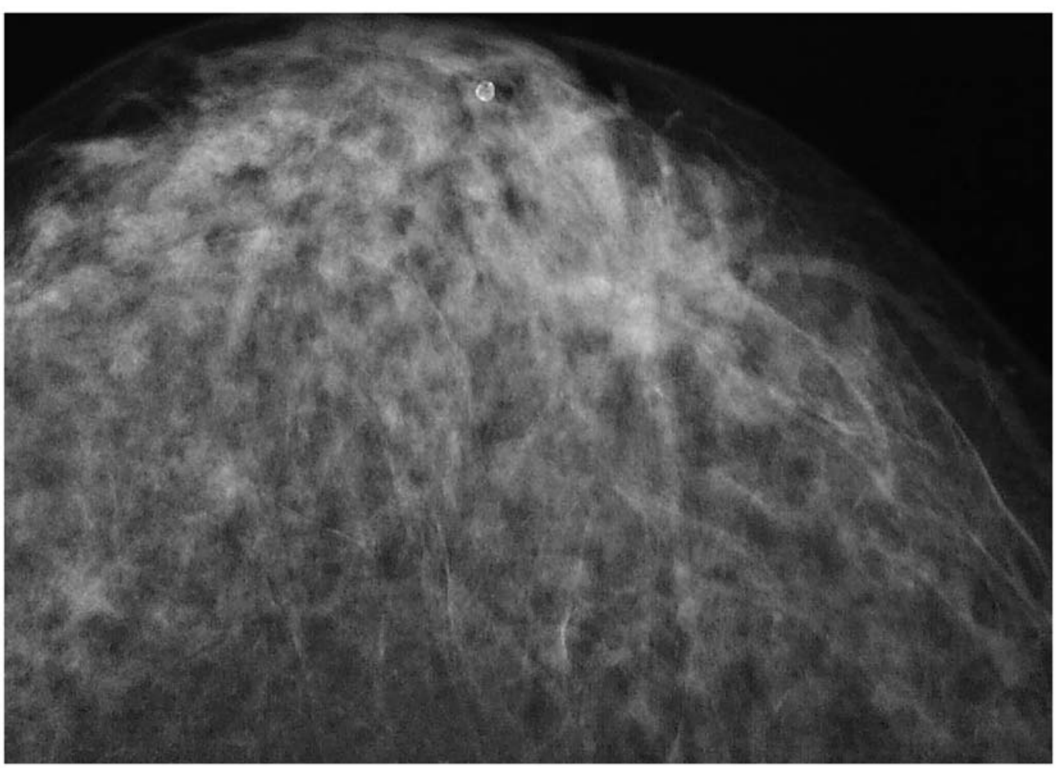

Figure 3. *Invasive ductal carcinoma presenting as architectural distortion on the mammogram.*

Table VI. *Correlations between the mammographic appearance and clinicopathologic features.*

	Mammographic appearance									
	Negative		Type A		Type B		Type C		Type D	
	n	*P*-value	n	*P*-value	n	*P*-value	n	*P*-value	n	*P*-value
Histological type	13		23		38		25		9	
IDC	10	>0.05	11	<0.01	37	<0.01	23	>0.05	8	>0.05
IDC+DCIS	3		12		1		2		1	
Menopausal status	13		23		38		25		9	
Premenopausal	10	>0.05	15	>0.05	16	<0.05	15	>0.05	6	>0.05
Postmenopausal	3		8		22		10		3	
Tumor size (cm)	12		22		37		23		8	
≤2	8	>0.05	9	>0.05	25	<0.05	6	<0.01	7	>0.05
>2	4		13		12		17		1	
Lymph node status	13		23		36		24		9	
Negative	9	>0.05	12	>0.05	23	>0.05	8	<0.05	7	>0.05
Positive	4		11		13		16		2	

Type: A: calcifications without an evident mass; B: masses without calcifications; C: evident mass with calcifications inside or outside of the mass; D: without a mass or calcification but with architectural distortion. IDC: Invasive ductal carcinoma; DCIS: ductal carcinoma *in situ*.

types ($p<0.01$). Patients presenting with Type B tumor on mammography were usually found to have unmixed IDC in histopathology ($p<0.01$), and tended to be postmenopausal ($p<0.05$). If the mass was accompanied by calcifications on the mammogram, the tumor size was frequently larger (>2cm). Axillary lymph node metastasis was also significantly related to mammographic mass accompanied by calcification ($p<0.05$). Sixty-seven percent (n=16) of cases with mammographic mass were accompanied by calcification and 37% (n=30) of all the other patients had positive axillary lymph nodes ($p<0.05$).

Tumors presenting as masses with or without calcifications on mammography were further divided into two groups, spiculated and non-spiculated, according to the marginal status. Twenty-seven masses had a spiculated margin, and 36 masses were non-spiculated. As shown in Table VII, the margin status was significantly related to molecular factors. Spiculated masses had a significantly higher ER-positive rate and PR-positive rate than non-spiculated masses (25/27, 92.59% *vs*. 23/36, 63.89%, $p<0.01$ and 25/27, 92.59% *vs*. 16/36, 44.44%, $p<0.01$, respectively). Significant correlations were also observed between Ki-67 positivity, overexpression of Her2 and spiculated margin status. On the contrary, the Ki-67 positivity of spiculated masses was lower than those that of non-spiculated masses (8/27, 29.63% *vs*. 30/36, 83.33%, $p<0.01$). In addition, the majority of spiculated masses were Her2 negative ($p<0.05$).

Table VII. *Correlation between spiculated margin and Immunohistochemistry status.*

Marker	Margin n(%) Non-spiculated	Spiculated	χ^2	*P*-value
Estrogen receptor				
Negative	13 (20.63%)	2 (3.17%)	7.0073	<0.01
Positive	23 (36.51%)	25 (39.68%)		
Progesterone receptor				
Negative	20 (31.75%)	2 (3.17%)	15.7384	<0.01
Positive	16 (25.40%)	25 (39.68%)		
Her2				
Negative	21 (33.33%)	23 (36.51%)	5.2814	<0.05
Positive	15 (23.81%)	4 (6.35%)		
Ki-67				
Negative	6 (9.52%)	19 (30.16%)	18.5905	<0.01
Positive	30 (47.62%)	8 (12.70%)		

Discussion

Mammography has become the most valuable diagnostic approach for breast lesions and has increased in frequency throughout the world, accompanied by the reduction of mortality of breast cancer. However, not all breast carcinomas can be detected by mammography, and patients whose tumors have a negative mammographic appearance usually have a poor prognosis. Mammographic features can help determine which appropriate surgery should be performed. For example, the absence of mammographic calcifications is important for breast-conserving surgery of primary breast cancer (14, 15). The ductal type is the most frequent histological variety amongst invasive breast carcinomas, and we exclusively selected IDC to explore possible relationships between mammographic appearances with clinical, pathological and biological characteristics.

High breast density was associated with a 1.8- to 6.0 fold increase in breast cancer risk (16, 17). Breast density is positively associated with stromal and epithelial cell proliferation, as well as some growth factors, such as insulin-like growth factor-1 (IGF-1), in premenopausal women (18, 19). We found that low breast density was associated with postmenopausal status, and age more than 50 years, with the proportion of mammographic mass in postmenopausal women being significantly higher than that in premenopausal women (47.83% *vs*. 25.81%, $p<0.05$). This difference may due to the decline of mammographic sensitivity for women with high breast density, especially in young women, with the tumor covered by pyknotic tissue. Our findings were consistent with a previous report that increased mammographic density may reduce mammographic sensitivity (20). Porter *et al*. found that tumors in fatty breasts were more likely to appear as indistinct or spiculated masses in contrast to that in dense breasts, which more commonly manifesting as architectural distortions (21).

Calcification was identified in 48 out of the 108 (44%) cases, comparable with previous reports (22, 23). On the contrary to other studies (24, 25), we did not find any relationship between calcification and menopausal status, or Her2 expression. This difference may due to the fact that the tumors of patients involved in our study were all IDC; we excluded pure DCIS, which was more likely to be Her2-positive or associated with premenopausal status. Calcification status was frequently observed in IDC with DCIS. In the 23 patients who showed only calcification on mammogram, 52% (12/23) had component of DCIS, significantly higher than the other types of mammographic appearance ($p<0.01$). Mammographic mass was frequently observed in tumors without DCIS ($p<0.01$). Mammographic calcification was thus associated with component of DCIS, while mammographic mass was correlated with pure IDC without DCIS. In addition, we found that a mammographically visible mass with calcification was more likely to be observed for tumor larger than 2 cm, consistent with previous findings by Gajdos *et al*. (26). Tumors appearing as calcifications on mammography were positively associated with axillary lymph node metastasis ($p<0.05$); further analysis showed that the lymph node-positive rate of tumors with only calcifications on mammography was not higher than that of other types (47.83% compared with 42.68%, $p>0.05$). Therefore, we conclude that calcification accompanied by mass on the mammogram is positively correlated with axillary lymph node metastasis of IDC.

The assessment of several molecular markers, such as hormone receptors, Her2 status, and Ki-67, have been demonstrated to contribute significantly to the management of breast carcinoma. In the present study, we focused on the relationship between mammographic spiculated mass and immunohistochemical markers ER, PR, Her2 and Ki-67. Our results showed that the tumors manifesting as spiculated mass on mammography were strongly associated with the positive expression of hormone receptors, Her2 negativity and lower proliferative activity as shown by Ki-67 labeling. Our findings may explain findings from previous reports that spiculated mass can predict good outcome and excellent prognosis (27-29). If the tumor has a spiculated margin on mammography but is hormone receptor-negative, we should consider it necessary to re-do the immunohistochemical staining in order to avoid patients not being offered endocrine therapy when indicated.

In conclusion, mammographic calcification accompanied by evident mass was correlated with larger tumor size and axillary lymph node metastasis. Tumors in patients presenting with spiculated mass showed positive hormonal receptor status, Her2 negativity and lower proliferative activity. Based on our current findings, the mammographic appearance reflects the biologic behavior of the breast tumor and should be taken into account when planning treatment for IDC.

Conflict of Interest

All the Authors have no conflict of interest to declare.

Acknowledgements

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