Chula Med J Vol. 59 No. 5 September- October 2015

Suspicious calcifications in BI-RADS 4 and 5 breast lesions: Digital mammographic-pathologic correlation

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Rattanathawornkiti K, Prueksadee J. Suspicious calcifications in BI-RADS 4 and 5 breast lesions: Digital mammographic-pathologic correlation. Chula Med J 2015 Sep – Oct;59(5): 471 - 87

Background : *The calcifications are commonly observed in mammographic feature of breast cancer. The assessment of combined descriptors of calcification may help predict the risk of malignancy.*

Objective : *To study the correlation and assess the accuracy of suspicious calcifications in BI-RADS 4 and 5 detected on digital mammography and pathology.*

Design : *Retrospective review*

Material and Methods : *Of 176 breasts with suspicious calcifications in BI-RADS 4 and 5 were reviewed the descriptors for morphology, distribution and other associated findings by using final category assessment by BI-RADS 5th edition. The definition was compared with histopathology from core needle biopsy or surgery.*

Setting : *Department of Radiology, King Chulalongkorn Memorial Hospital.*

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Results : *Forty-five benign (25.6%) and 131 malignant (74.4%) of 176 breast calcifications were confirmed. The positive predictive value (PPV) for malignancy according to BI-RADS were as follows: category 4A, 13/36 (36.1%); category 4B, 22/39 (56.4%); category 4C, 27/30 (90%) and category 5, 69/71(96.2%). PPVs for malignancy significantly increased in morphologic descriptors including amorphous, coarse heterogeneous, fine pleomorphic and fine linear descriptors were 51.7%, 81.2%, 84.6% and 91.4%, respectively. PPVs of distribution descriptors were 70.5% (79/112) of the cluster, 75% (6/8) of the regional, 76.5% (26/34) of the segmental and 90.9% (20/22) of the linear distribution.*

Conclusion : *Morphologic descriptors of suspicious calcifications were statistically significant increasing the risk of malignancy. The most and second most common PPVs of morphologic descriptors were fine linear and fine pleomorphic descriptors, respectively. The highest PPV of distribution descriptor was linear distribution.*

Keywords : *Suspicious calcification, BI-RADS 4 and 5, digital mammography, pathology.*

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Received for publication: February 6, 2015.

กิติรัตน์ รัตนถาวรกิติ, เจนจีรา ปรึกษาดี. ความสัมพันธ์ของลักษณะหินปูนที่น่าสงสัยในกลุ่ม BI-RADS 4 และ 5 ในภาพถ่ายแมมโมแกรมแบบดิจิตัลกับผลทางพยาธิวิทยา. จุฬาลงกรณ์เวชสาร 2558 ก.ย. – ต.ค.;59(5): 471 – 87

เหตุผลของการทำวิจัย : *หินปูนในแมมโมแกรม เป็นลักษณะที่พบได้บ่อยในมะเร็งเต้านม การประเมินลักษณะต่าง ๆ ของหินปูนเป็นสิ่งที่ช่วยทำนายโอกาสของการเกิดมะเร็งได้*

วัตถุประสงค์ : *เพื่อศึกษาความสัมพันธ์ และประเมินความถูกต้องของลักษณะหินปูนที่น่าสงสัย ในกลุ่ม BI-RADS 4 และ 5 ในการตรวจแมมโมแกรมเปรียบเทียบกับผลทาง พยาธิวิทยา*

รูปแบบการวิจัย : *การศึกษาข้อมูลย้อนหลัง*

วิธีการศึกษา : *ในผู้หญิง 172 ราย (เต้านม 176 ข้าง) ที่รับการตรวจแมมโมแกรมพบหินปูนที่น่าสงสัย และอยู่ในกลุ่ม BI-RADS 4 และ 5 ได้นำมาศึกษาโดยทบทวนลักษณะรูปร่าง การเรียงตัว ตำแหน่ง การกระจายตัวของหินปูน รวมทั้งลักษณะอื่นที่พบ เพื่อจำแนกกลุ่มตาม BI-RADS เปรียบเทียบกับผลทางพยาธิวิทยา*

สถานที่ทำการวิจัย : *ภาควิชารังสีวิทยา โรงพยาบาลจุฬาลงกรณ์*

ผลการศึกษา : *รอยโรคที่ไม่เป็นมะเร็ง 45 ราย และเป็นมะเร็ง 131 ราย คิดเป็นค่าพยากรณ์บวก (Positive predictive value (PPV)) 74.4% โดยแยกตามกลุ่มย่อยดังนี้ 4A,4B,4C และ 5 เป็นร้อยละ 36.1, 56.4, 90 และ 96.2 ตามลำดับ โอกาสเกิดมะเร็งเพิ่มมากขึ้นตามลักษณะรูปร่างของหินปูน ได้แก่ amorphous, coarse heterogeneous, fine pleomorphic และ fine linear descriptors ซึ่งคิด PPVs ได้เป็นร้อยละ 51.7, 81.2, 84.6 และ 91.4 ตามลำดับ PPVs ของการเรียงตัวของหินปูนในการเรียงตัวแบบ cluster, regional, segmental และ linear เป็น ร้อยละ 70.5, 75, 76.5 และ 90.9 ตามลำดับ*

สรุป : *ลักษณะรูปร่างของหินปูนที่น่าสงสัยมีโอกาสเกิดมะเร็งเต้านมเพิ่มมากขึ้นตามลักษณะรูปร่างและการเรียงตัวของหินปูน โดยที่มีโอกาสเกิดมะเร็งมากที่สุดคือรูปร่างและการเรียงตัวแบบ linear*

คำสำคัญ : *หินปูนที่น่าสงสัย, BI-RADS 4 และ 5, การตรวจแมมโมแกรม, ผลทางพยาธิวิทยา.*

In 2013, the American College of Radiology (ACR) developed the fifth edition of Breast Imaging Reporting and Data System (BI-RADS) which has been used to standardize mammographic reports and interpretations. Digital mammographic assessment categorization is divided into six categories. In addition, the fifth edition of BI-RADS provided category 4 lesions into three subdivisions according to small (category 4A), moderate (category 4B) and substantial (category 4C) likelihood of malignancy.[1, 2]

Calcifications in digital mammography are frequently presented. The features are used to determine whether or not the lesions are benign or malignant. The characteristics of morphology, distribution, size, number and variability are helpful to distinguish among the categories.[3]

From the prior study of microcalcification descriptors and categories in the fourth edition of BI-RADS can help predict the probability of malignancy for suspicious microcalcification.[4, 5] Although in BI-RADS microcalcification distribution descriptors are not divided into specific risk categories, they do help stratify the risk of malignancy. However, the use of combined descriptors may have a more powerful predictive ability than that of isolated descriptors.[5]

According to BI-RADS 5th edition 2013, the intermediate concern and high probability of malignancy were combined into suspicious morphology. There are also divisions of suspicious morphologic calcification into four groups that predict the risk of malignancy: amorphous, coarse heterogeneous, fine pleomorphic, and fine linear/ branching descriptor. The distribution of the calcifications is still described into diffuse, regional, cluster / grouped, segmental and linear distributions. The classifications of breast calcifications are reported according to the assessment of the morphology and distribution, that are the most and the second most important characteristics of calcifications.[2]

The upper outer quadrant (UOQ) of the breast is the most frequent site for incidence of breast cancer.[6, 7] The percentages are very similar for women from all ethnic groups and all ages.[6]Therefore the location descriptor also helps to define the probability of malignancy.

Mammographically detected non-palpable breast lesions often present as calcifications alone, calcifications with architectural distortion or calcifications associated with mass.[8, 9]

The study of calcifications in digital mammographic screening resulted in early detection of DCIS and invasive breast cancers more than film screening. Malignancies detected on the basis of calcifications, 38% were invasive cancers and 62% were DCIS.[10] In another study found 65% of malignant microcalcification lesions without a mass were DCIS, DCIS with a focus of invasion in 32% and invasive carcinoma only in 4%. [11] Invasive foci were more likely associated with mammographic calcification size of 11 mm and greater (40%, 77 from 194) compared with 1 - 10 mm (26%, 29 from 110), but increased extent of calcifications greater than 10 mm was not associated with greater likelihood of invasion.[11]

Microcalcification is the most common mammographic feature of DCIS, occurring in 80 - 96% with mammographic abnormality. In addition to the difference in calcification morphology, it has also been reported that the percentage of calcification in high grade DCIS was higher than in low grade DCIS (>90%

compared to 50 - 60%).[12] BI-RADS 4 breast lesions was mostly categorized for malignancies detected on calcifications for DCIS and invasive cancer.[4, 10] The many studies show the typically benign calcification or BI-RADS 2 and 3 categories not represent malignancy.[5, 13, 14]

The calcifications are commonly observed in invasive breast carcinomas in about 50% of study.[9] However, some suspicious microcalcification are benign, such as amorphous calcification found in 60% of fibrocystic changes, fibrosis, sclerosing adenosis, usual hyperplasia, fibroadenomas, benign stromal calcification, secretory change, duct papilloma and apocrine metaplasia,[8] as well as fibroadenomatoid hyperplasia.[15]

There are two types of calcification processes in the breast. The secretory type of calcification is an active mechanism related to secretion accumulation, likely to be found in benign lesions such as fibrocystic changes as well as low grade malignancies. The necrotic type of calcification is a passive mechanism occurs in the necrotic debris. It is seen in comedo necrosis of high grade DCIS.[9]

Even if the calcifications are clearly detected in mammography, multiple factors are responsible for missing the lesion. The most frequently suggested reasons for possible miss were dense breasts and distracting lesions. Others are calcification type, size and location.[16] Technical factors such as bad exposure, malposition and bad processing quality also cause miss interpretation.[17] The accuracy of mammographic interpretation among individual radiologists varies widely. The experience and training of radiologists were the main contributing factors.[18]

One of the main issues of radiologic pathologic correlation in breast calcification is the correct and adequate sampling of the calcification in question and the subsequent pathologic diagnosis.[8]

The retrospectively compared core biopsy diagnosis with surgical excision diagnosis in cores with and cores without calcification on specimen radiographs demonstrated that cores with calcification were more likely to enable a final diagnosis of malignancy than one another.[19] Radiography of core biopsy samples and histologic measurement of the size of calcification in core biopsy specimens is useful to reduce false-negative diagnoses in which a biopsy has been performed to evaluate mammographically suspicious calcifications.[20] The sensitivity of stereotactic core-needle biopsy was 82%[21] and multidisciplinary approach to include radiologist, pathologist, and surgeon were critical to ensure a thorough and accurate assessment of nonpalpable breast lesions.[22]

The purpose of this study was to evaluate the correlation and to assess the accuracy of suspicious calcifications in BI-RADS 4 and 5 detected on digital mammography and pathology.

Material and Method

Patient Selection:

Retrospective review of 16,577 women who underwent digital mammography at King Chulalongkorn Memorial Hospital from January 2012 to December 2012. Of 252 women with suspicious calcifications in their digital mammography and BI-RADS assessment, i.e., categories 4 or 5 were selected. Digital imaging data before procedure are available on Pictures Archiving and Communications System (PACs).

Sixty-three women were excluded because of unavailable histopathology on hospital electronic database and 17 cytopathology from fine needle aspiration (FNA) were also rejected. Of 172 women recruited and 4 had calcifications in both breasts; in total 176 breasts were in this study. The women were 31 - 92 years old at the time of mammography (mean age 53.2 years). The indication included screening 28 (16.3%), palpable mass 71 (41.3%), pain or inflammation 2 (1.1%) and follow-up lesions 71 (41.3%).

Histopathology were available on hospital electronic database, from core needle biopsy 17 (9.7%), excisional biopsy or wide excision 83 (47.2%) and mastectomy 76 (43.2%). Durations between perform mammography and final histopathology range from 0 - 319 days (mean duration 39.9 days). Most cases, 99/176 (56.25%), were operated within 1 month after mammography. Durations between 1 - 3 months were in 59 cases and 18 cases were more than 3 months.

Imaging acquisition and Processing:

All subjects received digital mammography with either a Hologic LORAD Selenia or a Hologic Selenia Dimensions at the Digital Mammography Unit. Mammography was obtained in two standard image planes, i.e. the craniocaudal (CC) and mediolateral oblique (MLO) views of the breast taken when both breasts were compressed on compression plate and film holder. The radiation dose was automatically calculated depending on the thickness of patient's breast. Additional planes such as spot magnification, cone compression or tomosynthesis, were performed in selected cases. All digital images were interpreted on screen at a high-resolution workstation.

Images interpretation

The digital mammography before biopsy or surgery was retrospectively interpreted with blinded clinical and histopathology report from PACs on work station. Standard functions were used for attentive the calcifications such as zoom, pan, magnification and adjust window levels.

Breast subspecialty radiologist regarding morphology, distribution, location and extension of the suspicious calcifications as well as the presence of associated findings and final assessment category by BI-RADS 5^{th} edition definition.

The morphology of calcifications was described as amorphous, coarse heterogeneous, fine pleomorphic, and fine linear/branching. The distribution of calcifications was described as diffuse/scatter distribution, regional distribution, cluster /grouped distribution, segmental distribution, and linear/ductal distribution. The extension of calcifications was assessed in 1 - 5 mm, 6 - 10 mm, 11 - 20 mm, 21 - 40 mm, and > 40 mm. The locations of calcifications were divided into upper inner, lower inner, upper outer, lower outer and subareolar / central regions. The associated findings included breast parenchymal density, associated hyperdense mass, architectural distortion, skin thickening/ nipple retraction and pathologic lymphadenopathy.

The final BI-RADS assessment BI-RADS categories were considered: category 4A,category 4B, category 4C, and category 5.

Data Analysis and Statistics

All selected cases were compiled on data collection form and their details recorded into three parts: patient information data, digital mammographic

data and histopathologic data. The data accumulation was stored and analysis by SPSS program version 22.

The data were analyzed between descriptors for suspicious calcifications in digital mammography and histopathology. As the outcomes of this study are nominal data, descriptive statistics were used as percentage that shows the correlation. Difference between categorical variables was used Chi-square test. Statistical significance will be determined as *p*-value less than 0.05 for all correlation and difference.

As for the results, they were found to be statistically significant; binary logistic regression was used to calculate the odds ratios and 95% CIs to assess the differences of malignancy between descriptors. Odds ratios were considered to indicate statistical difference if the 95% CI excluded 1.0.

Results

Histopathologic results

Of the176 calcification breasts, 45 (25.6%) were benign and 131 (74.4%) were malignant which representing overall positive predictive value for core needle biopsy, excisional biopsy or wide excision and mastectomy of 74.4%. The mean age of the benign and malignant were 51 years and 53.9 years, respectively.

According to pathology reports, there were 110 (62.5%) of mass and 66 (37.5%) of non-mass lesions. Ranging size of the masses was 3 - 85 mm (mean 29.5 mm). There were 17 benign and 93 malignant masses; the mean size of which mean size were 29.7 mm and 29.5 mm, respectively. Present of calcifications in 54 (30.7%) lesions and non-calcification in 122 (69.3%) were considered. No detail of the size or extension of calcification was reported.

The 45 benign lesions included 19 (42.2%) lesions of fibrocystic change, 17 (37.7%) lesions of proliferative disease, 6 (13.3%) of atypical ductal hyperplasia, two of fibroadenoma and one of inflammatory process. The 131 malignant lesions consisted of 27 (20.6%) lesions of pure DCIS with comedo necrosis, 46 (35.1%) lesions of ductal carcinoma in situ (DCIS) with invasive ductal carcinoma, 53 (40.5%) lesions of Invasive ductal carcinoma, two of invasive lobular carcinoma and three of mixed invasive ductal carcinoma.

The difference of subtypes of pathology and pathologic mass lesion were statistically significant (p <0.05) by chi-square test as shown in Table 1.

Digital Mammographic Findings and BIRADS Categories

The sites of calcification of 176 breasts were: right breast 94 (53.4%) and left breast 82 (46.6%).Most of calcification sizes were microcalcifications, 152 (86.4%) from 176 lesions. Of 24 (13.6%) lesions were considered macro-microcalcifications.

Breast parenchymal density was classified as fatty breast 2 (1.1%), scatter fibrograndular breast 41 (23.3%), heterogeneous dense123 (69.9%) and extremely dense10 (5.7%). There were suspicious calcification lesions associated with 80 (45.5%) hyperdense mass and 96 (54.5%) of non-mass lesions.

The amount of all lesions were found associated architectural distortion 10 (5.7%), skin thickening/ nipple retraction17 (9.6%) and pathologic lymphadenopathy 33 (18.8%).

The final BI-RADS assessment BI-RADS categories were as following: category 4A, 36 (20.5%); category 4B, 39 (22.2%); category 4C, 30 (17%) and category 5, 71 (40.3%) which positive predictive value for malignancy were category 4A, 13/36 (36.1%); category 4B, 22/39 (56.4%); category 4C, 27/30 (90%) and category 5, 69/71 (96.2%).The differences among categories and subcategories were statistically significant (p <0.001) and progressively increased from 4A to 5.

Morphology Descriptors of Calcifications

The morphology of 176 calcifications was described as amorphous 60 (34.1%), coarse heterogeneous 16 (9.1%), fine pleomorphic 65 (36.9%) and fine linear/branching 35 (19.9%).

Results of the chi-square test revealed a statistically significant difference among the morphologic descriptors (p <0.001). The detail of suspicious morphologic calcifications in each BI-RADS category is shown in Table 2. The probability of malignancy were also significantly increased, positivity predictive values of amorphous, coarse heterogeneous, fine pleomorphic and fine linear descriptors were 51.7%, 81.2%, 84.6% and 91.4%, respectively(Table 3).

The odds ratio of malignancy were 4.05 (95% CI: 1.05, 15.69) for coarse heterogeneous versus amorphous, 5.15 (95% CI: 2.22, 11.95) for fine pleomorphic versus amorphous, and 9.98 (95% CI: 2.75, 36.15) for fine linear versus amorphous (Table 4). Results of this analysis suggested that the coarse heterogeneous, fine pleomorphic and fine linear descriptors indicate significantly increased risk of malignancy (95% CI for odds ratios excluded 1, p < 0.05) compared with that of amorphous descriptor.

Distribution Descriptors of Calcifications

The distributions of 176 calcifications were described as diffuse distribution 0, regional distribution 8 (4.5%), clustered distribution 112 (63.6%),segmental distribution 34 (19.3%), and linear/ductal distribution 22 (12.5%).Positive predictive values were 75% (6/8) of regional, 70.5% (79/112) of cluster, 76.5% (26/34) of segmental, and 90.9% (20/22) linear distribution.

Results of the chi-square test and odds ratio of malignancy show no statistically significant difference among the distribution descriptors (p = 0.25)(Table 3).

Extension Descriptors of Calcifications

Extension of calcifications were assessed in 1 - 5 mm, 12 (6.8%); 6 - 10 mm, 31 (17.6%); 11 - 20 mm, 37 (21.0%); 21 - 40 mm, 52 (29.5%); and > 40 mm, 44 (25%). Positive predictive values for malignancy of calcification extension were as follows: 4/12 (33.3%) of 1-5 mm, 14/31 (45.2%) of 6 -10 mm, 33/37 (89.2%) of 11 - 20 mm, 41/52 (78.8%) of 21 - 40 mm, and 39/44 (88.6%) of > 40 mm. Chi-square test showed a statistically significant difference among the extension descriptors (p <0.001) (Table 3).

Location Descriptors of Calcifications

Location of calcifications were divided into 20 upper inner, 35 lower inner, 99 upper outer, 3 lower outer and 19 subareolar /central regions. Positive predictive values of location was as following; 14/20 (70%) of upper inner, 25/35 (71.4%) of lower inner,

70/99 (70.7%) of upper outer, 3/3 (100%) of lower outer, and 19/19 (100%) of subareolar /central region. There were no statistically significant difference among the location descriptors (p = 0.07) (Table 3).

Combined Descriptors of Calcifications

Details of PPVs for combined morphologic and distribution descriptors were shown in Table 5.Subgroup analysis of calcification descriptors and associated hyperdense mass for predict risk of malignancy used chi-square test, revealed statistically significant in group of morphologic calcification in non-mass (p <0.001), extension calcification in non-mass (p = 0.001) and extension of calcification in hyperdense mass (p = 0.033). Morphologic calcification in hyperdense mass was not statistically significant for malignant risk (p = 0.529)(Table 6).

For results of morphologic descriptor, extension descriptor and associated hyperdense mass found to be statistically significant, odds ratios and 95% Confidence Interval (CIs) were used to assess the differences of malignancy between descriptors.

Table 1. Histopathologic results.

Histopathology	Non-mass	Mass	Total
Benign	28	17	45
- Fibrocystic change	14	5	19
- Proliferative disease	8	9	17
- Atypical ductal hyperplasia	3	3	6
- Fibroadenoma	2	0	2
- Inflammation/abscess	1	0	1
Malignant	38	93	131
- DCIS with comedo necrosis	9	18	27
- DCIS with invasive ductal carcinoma	12	34	46
- Invasive ductal carcinoma	16	37	53
- Invasive lobular carcinoma	1	1	2
- Others	0	3	3
Total	66 (37.5%)	110 (62.5%)	176

Table 2. Rate of malignancy according to BI-RADS categories and morphologic descriptors.

Morphologic descriptors	BI-RADS category [No. of malignant / total (%)]				
	4A	4B	4C	5	Total
Amorphous	10/29	9/18	7/8	5/5	31/60 (51.7%)
Coarse heterogeneous	1/4	2/2	4/4	6/6	13/16 (81.2%)
Fine pleomorphic	2/3	5/11	9/11	39/40	55/65 (84.6%)
Fine linear	0/0	6/8	7/8	19/20	32/35 (91.4%)
Total	13/36	22/39	27/30	69/71	131/176

Table 3. Rate of malignancy according to descriptors of calcifications.

Descriptors of Calcifications	Benign	Malignant	Total	PPV (%)	*p*-value
Morphology of calcification					$p < 0.001$
- Amorphous	29	31	60	51.7	
- Coarse heterogeneous	3	13	16	81.2	
- Fine pleomorphic	10	55	65	84.6	
- Fine linear	3	32	35	91.4	
Distribution of calcification					$p = 0.25$
- Diffuse / scatter	0	0	0	0	
- Regional distribution	2	6	8	75.0	
- Grouped distribution	33	79	112	70.5	
- Segmental distribution	8	26	34	76.5	
- Linear distribution	2	20	22	90.9	
Extension of calcifications					$p < 0.001$
- 1 - 5 mm	8	4	12	33.3	
- 6 - 10 mm	17	14	31	45.2	
- 11 - 20 mm	4	33	37	89.2	
- 21 - 40 mm	11	41	52	78.8	
- > 40 mm	5	39	44	88.6	
Location of calcifications					$p = 0.07$
- Upper inner	6	14	20	70	
- Lower inner	10	25	35	71.4	
- Upper outer	29	70	99	70.7	
- Lower outer	0	3	3	100	
- Subareolar /central	0	19	19	100	
Associated Mass					$p < 0.001$
- None mass	39	57	96	59.4	
- Hyperdense mass	6	74	80	92.5	

Table 4. Risk of malignancy according to descriptors of calcifications pairs.

Descriptors of Calcifications	Odds ratio	95% CI	*p*-value
Morphology of calcification			
- Coarse heterogeneous versus amorphous	4.05	1.05 - 15.69	$p = 0.043$
- Fine pleomorphic versus amorphous	5.15	2.22 - 11.95	$p < 0.001$
- Fine linear versus amorphous	9.98	2.75 - 36.15	$p < 0.001$
Extension of calcifications			
- 6 - 10 mm versus 1 - 5 mm	1.65	0.41 - 6.63	$p = 0.483$
- 11-20 mm versus 1-5 mm	16.50	3.38 - 80.64	$p = 0.001$
- 21-40 mm versus 1-5 mm	7.46	1.89 - 29.41	$p = 0.004$
- > 40 mm versus 1-5 mm	15.60	3.42 - 71.26	$p < 0.001$
Associated Mass			
- Hyperdense mass versus non-mass	8.44	3.34 - 21.31	$p < 0.001$

Table 5. Rate of malignancy according to combined morphology & distribution of calcifications.

Morphology	Distribution [No. of malignant / total (%)]					
	Diffuse	Regional	Cluster	Segmental	Linear	Total
Amorphous	NA	2/4	24/46	5/10	NA	31/60 (51.6)
Coarse heterogeneous	NA	2/2	10/13	1/1	NA	13/16 (81.3)
Fine pleomorphic	NA	1/1	38/46	13/15	3/3	55/65 (84.6)
Fine linear	NA	1/1	7/7	7/8	17/19	32/35 (91.42)
Total	NA	6/8 (75)	79/112 (70.5)	26/34(75.8)	20/22 (90.5)	

Table 6. Rate of malignancy according to descriptors associated with mass.

Descriptors of Calcifications	Benign (%)	Malignant (%)	Total	*p*-value
Morphology of calcification in Non-mass	39 (40.6)	57 (59.4)	96	$p < 0.001$
- Amorphous	26 (66.7)	13 (33.3)	39	
- Coarse heterogeneous	3 (33.3)	6 (66.7)	9	
- Fine pleomorphic	8 (24.2)	25 (75.8)	33	
- Fine linear	2 (13.3)	13 (86.7)	15	
Morphology of calcification in mass	6 (7.5)	74 (92.5)	80	$p = 0.529$
- Amorphous	3 (14.3)	18 (85.7)	21	
- Coarse heterogeneous	0	7 (100)	7	
- Fine pleomorphic	2 (6.2)	30 (93.8)	32	
- Fine linear	1 (5.0)	19 (95)	20	

Table 6. Rate of malignancy according to descriptors associated with mass. (Continuous)

Descriptors of Calcifications	Benign (%)	Malignant (%)	Total	*p*-value
Extension of calcifications in Non-mass	39 (40.6)	57 (59.4)	96	$p = 0.001$
- 1 - 5 mm	8	3	11	
- 6 - 10 mm	15	11	26	
- 11 - 20 mm	3	16	19	
- 21 - 40 mm	11	13	24	
- > 40 mm	2	14	16	
Extension of calcifications in mass	6 (7.5)	74 (92.5)	80	$p = 0.033$
- 1 - 5 mm	0	1	1	
- 6 - 10 mm	2	3	5	
- 11 - 20 mm	1	17	18	
- 21 - 40 mm	0	28	28	
- > 40 mm	3	25	28	
Distribution of calcification in Non-mass				$p = 0.237$
Distribution of calcification in Hyperdense mass				$p = 0.739$
Location of calcifications in Non-mass				$p = 0.161$
Location of calcifications in Hyperdense mass				$p = 0.681$

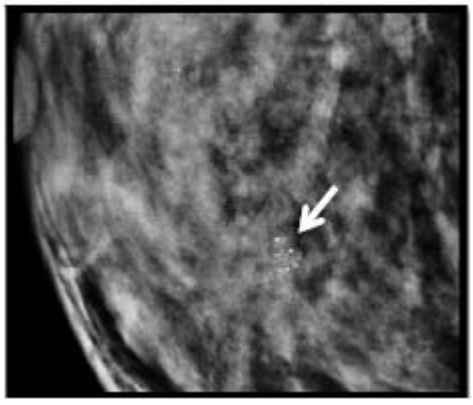

Figure 1. Right breast CC view in a 45-year-old woman showing cluster of fine pleomorphic microcalcification (arrow) at right lower inner quadrant: BI-RADS 4B. Histopathology was invasive ductal carcinoma.

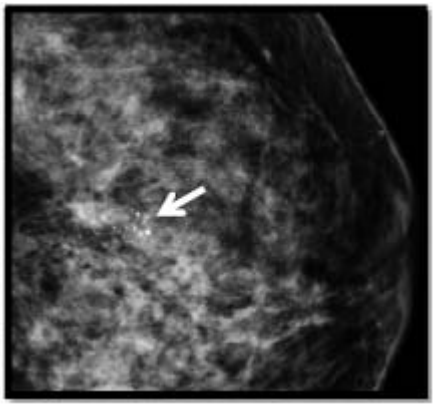

Figure 2. Left breast CC view in a 52-year-old woman showing cluster of coarse heterogeneous calcification (arrow) at left upper outer quadrant: BI-RADS 4C. Histopathology was invasive lobular carcinoma.

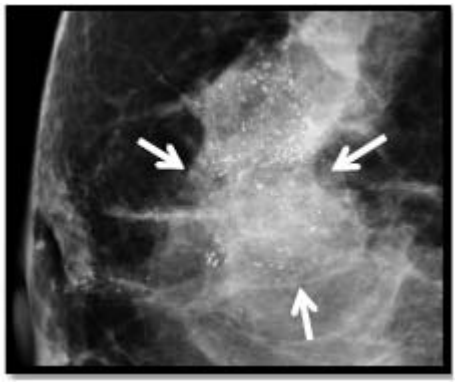

Figure 3. Right breast CC view in a 40-year-old woman showing fine pleomorphic microcalcifications with segmental distribution (arrow) without mass at right upper outer quadrant: BI-RADS 5. Histopathology was invasive ductal carcinoma with extensive DCIS.

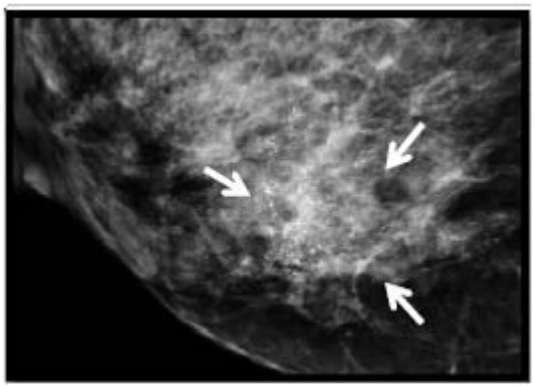

Figure 4. Right breast MLO view in a 46-year-old woman showing fine linear microcalcifications with segmental distribution (arrow) associated with ill-defined hyperdense mass at right lower inner quadrant: BI-RADS 5. Histopathology was atypical ductal hyperplasia.

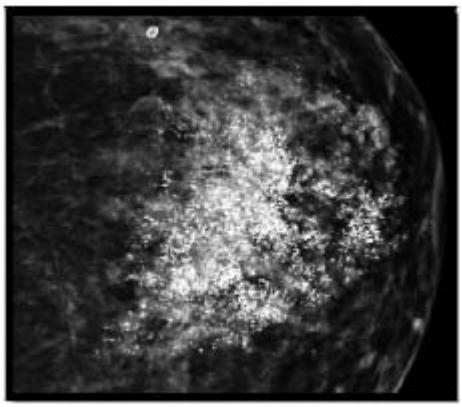

Figure 5. Left breast CC view in a 59-year-old woman showing fine linear microcalcifications with regional distribution, without mass at left upper inner quadrant: BI-RADS 5. Histopathology was invasive ductal carcinoma with extensive DCIS.

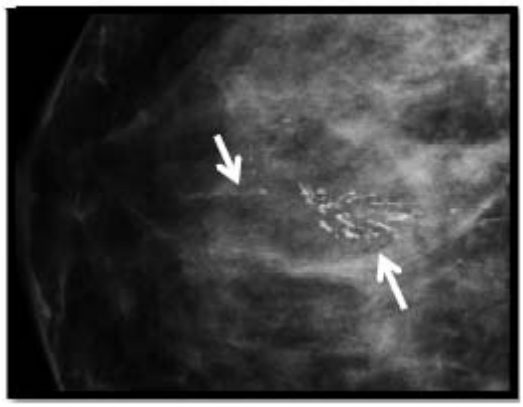

Figure 6. Right breast CC view in a 47-year-old woman showing fine linear microcalcifications with linear branching distribution (arrow) without mass at right subareolar region: BI-RADS 5. Histopathology was ductal carcinoma in situ with comedo necrosis

Discussion

Overall positive predictive value for core needle biopsy, excisional biopsy or wide excision and mastectomy is 74.7% which is more than the overall positive predictive value for biopsy found in previous studies of 12.3 - 47 %.[4, 5, 13, 14]

In the BI-RADS final assessment category, the guidance range of malignancy likelihood should be 2 - 10% in category 4A, 11 - 50% in category 4B, 51 - 95% in category 4C and >95% in category 5. Our results for PPVs of category 4A (36.1%) and 4B (56.4%) were higher expected range. However, our

results for BI-RADS 4C (90%) and 5 (96.2%) were in the expected range as well as the PPVs for each BI-RADS final assessment score and subdivision were progressively increased from 4A to 5.

According to BI-RADS 5th edition 2013, the morphology of intermediate concern and high probability of malignancy were combined into suspicious morphology. In our study, we found that the morphology descriptors can help predict the risk of malignancy for suspicious calcification which progressive risk of malignancy among descriptors; amorphous, course heterogeneous, fine pleomorphic and fine linear / branching descriptors, that of agree with those of previous studies.[4, 5, 13, 14]

The most and second most PPVs for malignancy of morphology descriptor was fine linear (91.4%) and fine pleomorphic (84.6%), consistent with previously report values of 53 - 91% by Burnside ES and Shin HJ, and 18.2 - 86% by Youk JH and Shin HJ, respectively.[4, 5, 13, 14]

For amorphous and coarse heterogeneous descriptors were distributed PPVs. Our study has PPV of amorphous 51.7% and PPV of coarse heterogeneous 81.2% which higher than the previous study results shown that PPV of amorphous 6.5 - 31% by Youk JH and Shin HJ, and PPV of coarse heterogeneous 7 - 31% by Burnside ES and Shin HJ.[4, 5, 13, 14]

The chances of malignancy were also different depending on their distribution from prior study. The most PPV for malignancy of extension descriptor was linear distribution (90.9%), consistent with previously report values of 67 - 83% by Burnside ES and Shin HJ.[4, 5, 14] The second most PPV for malignancy of extension descriptor was segmental distribution (76.5%), concomitant with the previous studies (30 - 81%) by Youk JH and Shin HJ.[4, 5, 14] Bent CK *et al*.[13] made a distinction of PPVs for malignancy, shown the most PPV was segmental distribution (56%) and the second most PPV was linear distribution (50%).

Our PPVs for malignant of regional (75%) and cluster (70.5%) distributions were higher range than all prior studies, ranged from 0 - 14% by Burnside ES and Shin HJ, and 9.1 - 38% by Youk JH and Shin HJ, respectively.[4, 5, 13, 14] Thus, the distribution descriptor of our study was no statistically significant to predict malignancy.

Stomper PC *et al.*[11]reported that invasive foci of malignant calcifications were more associated with mammographic calcification size of 11 mm and greater (40%, 77/194), compared with 1-10 mm (26%, 29/110) statistically significant (p = 0.019). In our results of extension of calcification was also statistically significant and increase risk of malignancy in the extension more than 10 mm (84.9%, 113/133).

The most location of suspicious calcification was seen in the right upper outer quadrant 70/99 (70.7%) and the most PPV for malignancy of location was the lower outer 3/3 (100%), and subareolar / central regions 19/19 (100%).

In present study shown suspicious calcification lesions associated with 80 (45.5%) hyperdense masses and 96 (54.5%) of non-mass lesions. After subgroup analysis of calcification descriptors and associated hyperdense mass for predict risk of malignancy revealed statistically significant in group of morphologic calcification in non-mas (p <0.001), extension calcification in non-mass (p = 0.001) and extension of calcification

in hyperdense mass (p = 0.033). The morphologic calcification of hyperdense mass was not statistically significant of malignant risk (p = 0.529).Consequently suspicious calcification helps predict the risk of malignancy especially when there is no associated mass lesion.

The highest PPVs of combined descriptors for suspicious calcifications in our study were fine linear morphology with linear distribution representing malignancy for 17 (89.5%) of 19 cases, fine pleomorphic with segmental distribution for 13 (86.6%) of 15 cases, and fine pleomorphic with cluster distribution for 38 (82.6%) of 46 cases.

Limitation

There were a few limitations in the present study. First, retrospective analysis was used and selection bias of patient populations. It would be prospectively evaluated the positive predictive value of each descriptor and the combined descriptors of suspicious calcifications. Second, our study was reviewed by only one radiologist and evaluation of intraobserver variability was not done; more radiologists' interpretation interobserver variability would bring more accuracy. Third, the small number of patients in present study with large number of malignancy causing higher positive predictive values for malignancy than expected outcome.

Conclusion

Morphologic descriptors of suspicious calcifications were statistically significant progressively increasing the risk of malignancy. The most and second most common PPVs of morphologic descriptors were fine linear and fine pleomorphic descriptors, respectively. The highest PPV of distribution descriptor was linear distribution and suspicious calcifications associated with hyperdense mass also increased the chance of malignancy than microcalcifications alone.

References

1. D'Orsi CJ, Bassett LW, Berg WA, Beam CA, Lewis RS, Crewson PE. Breast Imaging Reporting and Data System (BI-RADS): ACR BI-RADS mammography. 4th ed. Reston, VA: American College of Radiology, 2003
2. Sickles EA, D'Orsi CJ, Bassett LW, Appleton CM, Berg WA, Burnside ES, Feig SA, Gavenonis SC, Newell MS, Trinh MM. Breast Imaging Lexicon - mammography: calcification. In: D'Orsi CJ, ed. ACR BI-RADS Atlas Breast Imaging Reporting and Data System. 5th ed. Reston, VA: American College of Radiology, 2013: 37-78
3. Picca DA, Paredes ES. Calcifications in the breast: a radiologic perspective. Appl Radiol 2003 Sep: 32(9):29-37
4. Youk JH, Son EJ, Kim JA, Moon HJ, Kim MJ, Choi CH, Kim EK. Scoring system based on BI-RADS lexicon to predict probability of malignancy in suspicious microcalcifications. Ann Surg Oncol 2012 May;19(5):1491-8
5. Burnside ES, Ochsner JE, Fowler KJ, Fine JP, Salkowski LR, Rubin DL, Sisney GA. Use of microcalcification descriptors in BI-RADS 4th edition to stratify risk of malignancy. Radiology 2007 Feb; 242(2):388-95
6. Morris CR, Kwong SL, eds. Breast Cancer in California, 2003. Sacramento, CA: California

Department of Health Services, Cancer Surveillance Section, 2004

7. Darbre PD. Recorded quadrant incidence of female breast cancer in Great Britain suggests a disproportionate increase in the upper outer quadrant of the breast. Anticancer Res 2005 May; 25(3c):2543-50
8. Tse GM, Tan PH, Cheung HS, Chu WC, Lam WW. Intermediate to highly suspicious calcification in breast lesions: a radio-pathologic correlation. Breast Cancer Res Treat 2008 Jul;110(1):1-7
9. Tse GM, Tan PH, Pang AL, Tang AP, Cheung HS. Calcification in breast lesions: pathologists' perspective. J Clin Pathol 2008 Feb;61(2): 145-51
10. Weigel S, Decker T, Korsching E, Hungermann D, Bocker W, Heindel W. Calcifications in digital mammographic screening: improvement of early detection of invasive breast cancers? Radiology 2010 Jun;255(3): 738-45
11. Stomper PC, Geradts J, Edge SB, Levine EG. Mammographic predictors of the presence and size of invasive carcinomas associated with malignant microcalcification lesions without a mass. AJR Am J Roentgenol 2003 Dec;181(6):1679-84
12. Evans A, Pinder S, Wilson R, Sibbering M, Poller D, Elston C, Ellis I. Ductal carcinoma in situ of the breast: correlation between mammographic and pathologic findings. AJR Am J Roentgenol 1994 Jun;162(6): 1307-11
13. Bent CK, Bassett LW, D'Orsi CJ, Sayre JW. The positive predictive value of BI-RADS microcalcification descriptors and final assessment categories. AJR Am J Roentgenol 2010 May;194(5):1378-83
14. Shin HJ, Kim HH, Ko MS, Kim HJ, Moon JH, Son BH, Ahn SH. BI-RADS descriptors for mammographically detected microcalcifications verified by histopathology after needle-localized open breast biopsy. AJR Am J Roentgenol 2010 Dec;195(6):1466-71
15. Kamal M, Evans AJ, Denley H, Pinder SE, Ellis IO. Fibroadenomatoid hyperplasia: a cause of suspicious microcalcification on mammographic screening. AJR Am J Roentgenol 1998 Nov;171(5):1331-4
16. Birdwell RL, Ikeda DM, O'Shaughnessy KF, Sickles EA. Mammographic characteristics of 115 missed cancers later detected with screening mammography and the potential utility of computer-aided detection. Radiology 2001 Apr;219(1):192-202
17. Kamal RM, Abdel Razek NM, Hassan MA, Shaalan MA. Missed breast carcinoma; why and how to avoid? J Egypt Natl Canc Inst 2007 Sep;19(3):178-94
18. Majid AS, de Paredes ES, Doherty RD, Sharma NR, Salvador X. Missed breast carcinoma: pitfalls and pearls. Radiographics 2003 Jul; 23(4):881-95
19. Margolin FR, Kaufman L, Jacobs RP, Denny SR, Schrumpf JD. Stereotactic core breast biopsy of malignant calcifications: diagnostic yield of cores with and cores without calcifications on specimen radiographs. Radiology 2004 Oct;233(1):251-4

20. DahIstrom JE, Sutton S, Jain S. Histologic-radiologic correlation of mammographically detected microcalcification in stereotactic core biopsies. Am J Surg Pathol 1998 Feb; 22(2):256-9
21. Han BK, Choe YH, Ko YH, Nam SJ, Kim JH, Yang JH. Stereotactic core-needle biopsy of non-mass calcifications: outcome and accuracy at long-term follow-up. Korean J Radiol 2003;4(4):217-23
22. Fuhrman G, Cederbom G, Champagne J, Farr G, McKinnon W, Bolton J, Ordoyne WK. Stereotactic core needle breast biopsy is an accurate diagnostic technique to assess nonpalpable mammographic abnormalities. J La State Med Soc 1996 Apr;148(4):167-70