Original Article
pISSN 1738-2637
J Korean Soc Radiol 2011;65(6):595-601

대한영상의학회지

Clinical Significance and Pathologic Outcomes of Coarse Heterogeneous Calcifications Detected on a Mammography[1]

유방촬영술에서 발견된 거친 비균질성 석회화의 임상적 의의와 병리 소견의 고찰[1]

Hyun-ju Lim, MD[1], Kyu-Ran Cho, MD[1], Bo Kyung Seo, MD[1], Ok Hee Woo, MD[1], Kyu Won Hwang, MD[1], Yu Whan Oh, MD[1], Jeoung Won Bae, MD[2], Kyung Hwa Park, MD[3]

Departments of [1]Radiology, [2]Surgery, [3]Oncology, Korea University College of Medicine, Seoul, Korea

Purpose: To investigate the clinical significance and pathologic outcome of coarse heterogeneous calcifications (CHCs) detected on a mammography.

Materials and Methods: A retrospective review of our institutional mammographic database revealed 65 women with CHCs. Of these, we included 27 with pathologic verification (n = 27; benign in 13, malignancy in 14). Mammograms were interpreted in terms of CHC distribution (clustered, linear, segmental, regional, or diffuse), the area of CHCs, and associated findings. We also evaluated the presence of mass, ductal change, or change of parenchymal echogenicity on ultrasound images (n = 26). We correlated and statistically analyzed the radiologic features with pathologic findings.

Results: The individual distributional descriptors of CHCs predicted the risk of malignancy as follows: clustered (8/22); linear (1/2); regional (0/1); segmental (5/5). The segmental distribution predicted malignancy ($p < 0.05$). The CHC area in malignant lesions was larger than that of benign lesions ($p < 0.05$). Mammography revealed an associated mass in 2 out of 13 benign and 5 out of 14 malignancies. However, an increased risk of malignancy was not shown by the presence of an associated mass and its larger size. Ultrasound findings were not significant for predicting malignancy.

Conclusion: CHCs were verified as malignancy in 52% of cases, especially when characterized by segmental distribution and larger CHC areas on mammography.

Index terms
Coarse Calcification
Mammography
Breast
Breast Cancer
Diagnosis

Received July 27, 2011; **Accepted** September 19, 2011
Corresponding author: Kyu-Ran Cho, MD
Department of Radiology, Korea University Anam Hospital, Korea University College of Medicine, 126-1 Anam-dong 5-ga, Seongbuk-gu, Seoul 136-705, Korea.
Tel. 82-2-929-5578 Fax. 82-2-929-3796
E-mail: krcho@korea.ac.kr

INTRODUCTION

Mammography is widely used as a screening and diagnostic tool for detection and characterization of breast lesions. American College of Radiology (ACR) recommends the breast imaging reporting and data system (BI-RADS) for adequate categorization and management of findings on mammography. The BI-RADS lexicon contains guidelines for characterizing microcalcifications based on their morphology and distribution on mammography (1).

In 2003, the BI-RADS 4th edition was published and a previous pleomorphic descriptor was divided in two-coarse heterogeneous and fine pleomorphic. The coarse heterogeneous descriptor is defined as "irregular, conspicuous calcifications, generally larger than 0.5 mm" and they are included in the intermediate concern category with amorphous microcalcifications. By contrast, the fine pleomorphic descriptor describes microcalcifications that "vary in sizes and shapes, usually less than 0.5 mm in diameter" and are considered to have a higher probability of malignancy (2).

Burnside et al. (3) studied the risk of malignancy of the microcalcification morphological descriptors. The results in increasing risk order were benign, coarse heterogeneous, amorphous, fine pleomorphic, and fine linear. However, according to the study by Chan et al. (4), coarse heterogeneous calcifications had a higher risk of malignancy than amorphous calcifications.

Although microcalcification distribution descriptors are not divided into specific risk categories in the BI-RADS (2), the distribution of calcifications has been reported to be associated with the risk of malignancy, with increasing levels of risk proceeding from diffuse or scattered, regional, clustered linear to segmental distribution (5).

Despite previous studies on microcalcification morphology with or without distribution descriptors, the data focusing on coarse heterogeneous calcifications (CHCs) are sparse. To date, there have been no published reports dedicated to this subject, to our knowledge. The purpose of this study was to investigate the clinical significance and pathologic outcomes associated with coarse heterogeneous microcalcifications detected on mammography.

MATERIALS AND METHODS

A retrospective review of our institutional database was performed to identify all mammographic examinations with CHCs noted in the radiologic report. A total of 76 screening or diagnostic mammograms showing CHCs were identified during this period.

Two experienced breast radiologists (10 years and 13 years), both of whom were blinded to the pathologic results, reviewed the shape of the microcalcifications by consensus. Of the 76 cases, 11 cases were excluded because they showed dystrophic or mixed pleomorphic morphology rather than CHCs. A total of 65 mammograms were finally included in this study.

Patient Selection

Inclusion criteria for this study consisted of all CHCs detected on mammography that subsequently underwent pathologic confirmation by image guided core needle biopsy or excisional biopsy. From a total of 65 patients, we included 27 with pathologic verification in this study. Pathologic diagnoses were obtained by imaging-guided biopsy (n = 19) or excisional biopsy (n = 8). Among them, mammograms were available from all 27 women and a breast ultrasonography was performed in 26 cases. A detailed pathology of each lesion was extracted from the clinical data base.

In this study, malignancy was defined as the pathologic diagnosis of invasive carcinoma, ductal carcinoma in situ, or metastasis. High risk lesions, including atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ, were considered benign for the statistical analysis. All patients with these high risk lesions were followed up with an excisional biopsy and their surgical results were used as a reference standard.

For patients with microcalcifications identified as benign on biopsy, a follow up by subsequent mammography was performed at least 12 months after the biopsy to ascertain whether a patient had carcinoma.

Imaging and Evaluation

Digital mammographic examinations were performed with either a Lorad/Hologic Selenia Full Field Digital Mammography System (Lorad/Hologic, Danbury, CT, USA) or a Senographe 200D (General Electric Medical Systems, Milwaukee, WI, USA) full field digital mammography unit. Two experienced breast radiologists (10 years and 13 years), both of whom were blinded to the pathologic results, interpreted the digital mammograms of these patients for distribution (clustered, linear, segmental, regional, and diffuse), size of the CHCs (recorded as the longest diameter of the CHC lesion areas), presence of the associated mass, and mass size by consensus. BI-RADS final assessment categorization of each lesion was performed by the review of two radiologists by consensus. We also reviewed the ultrasound findings performed consecutively (within 1 month from mammography) at the corresponding area of CHCs on mammography and analyzed for the following criteria: presence of mass, ductal change at or adjacent to the lesion, and change in parenchymal echogenicity. According to the BI-RADS (2), 'ductal change' was defined as an abnormal caliber and/or arborization.

Statistical Analysis

We used the statistical program SPSS (version 12.0; SPSS Inc., Chicago, IL, USA) to conduct the statistical analyses. Tests for statistical significance were performed using Fisher's exact test (categorical values) or the Mann-Whitney test (continuous variables). The population proportion test was later used to assess the CHC distribution descriptor. Statistical significance was defined as a two-tailed p-value of < 0.05. The statistical analysis of the data was supervised by a biostatistician from our institution.

RESULTS

The age of the 27 patients ranged from 28 to 72 years (mean,

47.0 years). Lesions included in this study were identified on mammographies conducted for clinical indications as follows: screening in 7, palpable mass in 4, nipple discharge in 1, change in annual imaging follow up in 5, and an abnormal finding on the outside mammography in 10 patients.

Overall results are shown in Table 1, and this includes the 27 cases with pathologic results. The 14 (52%, 14/37) "pathologically proven" malignancies consisted of 5 (36%) invasive ductal carcinomas, 8 (57%) ductal carcinomas in situ (DCIS) and 1 metastatic carcinoma (adenocarcinoma from the stomach). Of the 13 (48%, 13/27) pathologically proven benign lesions, there were 7 (54%) with fibrocystic change, 3 (23%) with atypical ductal hyperplasia, 1 with papilloma, 1 with fibroadenoma and 1 with focal fibrosis.

Mammographic Characteristics

The mammographic features of benign and malignant CHCs from our study population are summarized in Table 1.

Distribution and Size of CHCs

From our results, CHCs were associated with malignancy in 52% of cases. Eight (42%) of 19 clustered, (50%) of 2 linear, and 5 (100%) of 5 segmental CHCs represented malignancy. Of the 13 benign lesions, clustered distribution was most frequent (11, 84%). On a side note, 1 linear (8%) and 1 regional distribution (8%) were also observed in the benign cases. The population proportion method was used to assess the differences among the CHC distribution descriptors with respect to the risk of malignancy. The segmental distribution was significantly predictive of malignancy ($p = 0.048$) in this study.

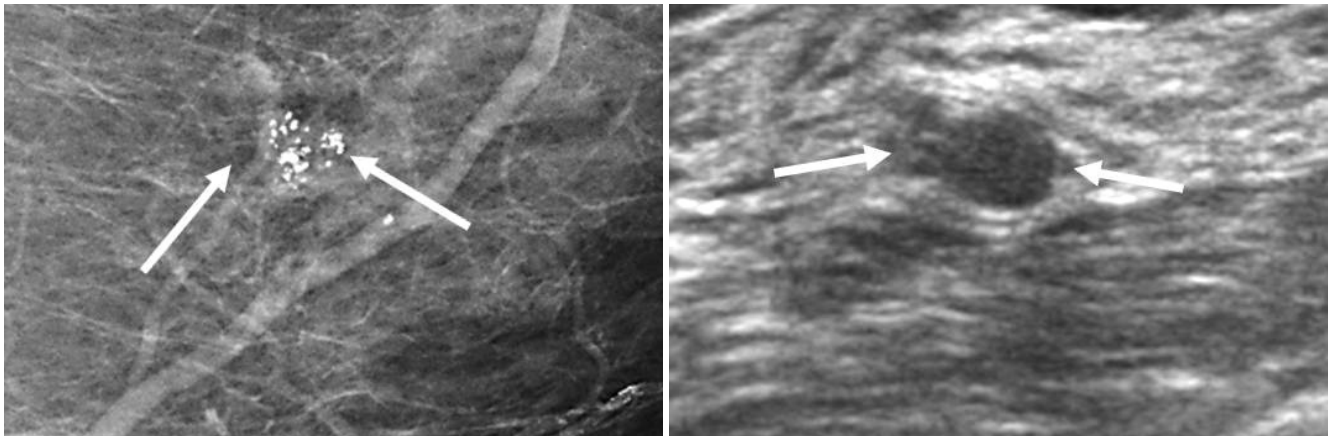
The longest diameter of the CHC area was also measured on mammography. The mean diameter was 1.8 cm (range: 0.3-7.2 cm) in benign and 3.7 cm (range: 0.6-8.7 cm) in malignant lesions. The Mann-Whitney test showed a statistically significant difference in size of CHC area between benign and malignant lesions ($p = 0.022$, range: 3.4-87.0).

Associated Mass, Mean Size, Margin, Shape

Of the 13 benign lesions, only 2 (15%) were accompanied by a mass on mammography with a mean diameter of 0.75 cm (range 0.5-1.0 cm) (Fig. 1). Among 14 malignant lesions, there were 5 (36%) with a mass on mammography with a mean diameter of 2.7 cm (range 1.5-5.1 cm). Comparison of these mass-

Table 1. Mammographic Findings in 27 Cases with Coarse Heterogeneous Calcifications

Mammographic Findings ($n = 27$)	Benign ($n = 13$)	Malignant ($n = 14$)
Presence of an associated mass	2 (15%)	5 (36%)
Mean mass size	0.75 cm	3.0 cm
Distribution of calcifications		
Clustered	11 (84%)	8 (57%)
Linear	1 (8%)	1 (7%)
Regional	1 (8%)	0 (0%)
Segmental	0 (0%)	5 (36%)
Diffuse	0 (0%)	0 (0%)



A B

Fig. 1. A 50-year-old woman with pathologically proven fibrocystic change.
A. Mammogram shows an approximately 1 cm sized relatively oval-shaped isodense mass with clustered coarse heterogeneous calcifications (arrows) in the upper central portion of the left breast.
B. On breast sonography, this lesion is about 1.2 cm in size with an indistinctly margined hypoechoic mass (arrow).

es showed substantial differences between shape and margins, in terms of benign versus malignant. An irregular shape and/or obscured, spiculated margins were more characteristic of a malignant lesion.

According to the assessment with Fisher's exact test, the presence of a mass did not predict malignancy ($p = 0.385$). Also, results of the Mann-Whitney test suggested that larger mass size does not indicate a significantly increased risk of malignancy ($p = 0.095$).

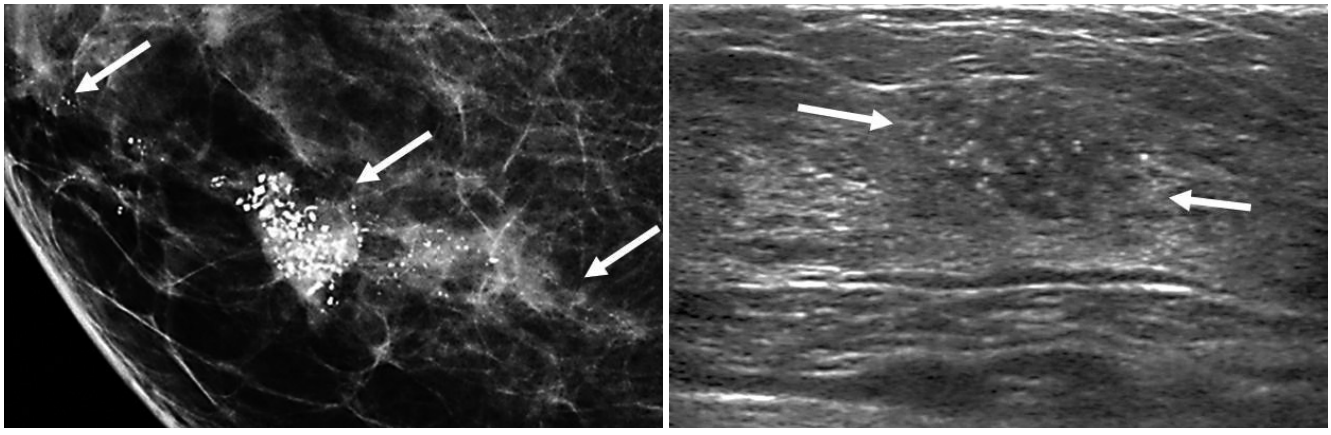
Table 2. Breast Ultrasonographic Findings of 26 Cases with Coarse Heterogeneous Calcifications

Ultrasonographic Findings (n = 26)	Benign (n = 13)	Malignant (n = 13)
Presence of an associated mass	5 (38%)	6 (46%)
Ductal change	1 (8%)	2 (15%)
Hypoechoic parenchymal change	1 (8%)	3 (23%)

Ultrasonographic Characteristics

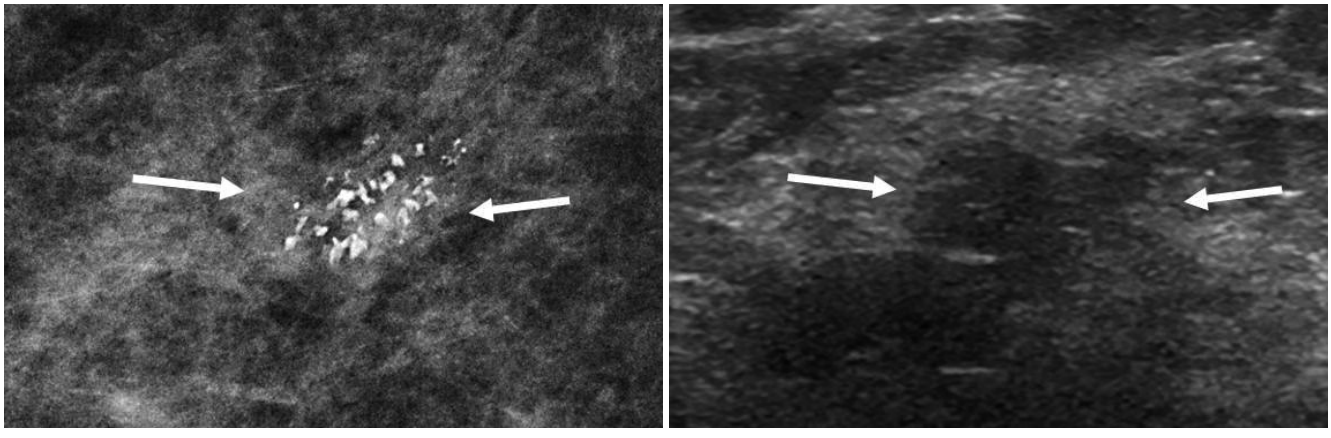
Table 2 lists results from 26 patients in which consecutive ultrasonographic evaluations were available. Of the 13 benign lesions seen on ultrasonography, 5 (38%) presented with associated mass, 1 with focal ductal ectasia accompanied by microcalcifications (which was proven to be fibrosis on biopsy) and 1 with parenchymal echo change.

Among 14 patients with malignant pathology, breast ultrasonography was performed in 13 of them. Further, 6 (46%) were accompanied by a mass (Fig. 2) and 2 revealed ductectasia with periductal infiltration (15%). Parenchymal distortion or ill defined hypoechoic areas were noted in 2 cases (23%), which



A B

Fig. 2. A 41-year-old woman with pathologically proven ductal carcinoma *in situ*.
A. On mammogram, linear and clustered coarse heterogeneous microcalcifications (arrows) are seen in the right mid inner portion.
B. On breast ultrasonography, an indistinct oval-shaped hypoechoic mass with associated calcifications (arrows) is seen in the right breast.



A B

Fig. 3. A 47-year-old woman with pathologically proven microinvasive ductal carcinoma in situ.
A. On magnification mammogram, coarse heterogeneous microcalcifications (arrows) are found to be clustered in right upper inner quadrant.
B. On breast sonography, a 1.1 × 0.8 cm-sized hypoechoic mass (arrows) is seen at a corresponding location.

were confirmed as DCIS (Fig. 3). However, the Fisher's exact test showed that differences in ultrasonographic findings were not statistically significant in predicting malignancy.

DISCUSSION

Microcalcifications are a very important finding in asymptomatic patients with early breast cancer. Approximately 30% to 50% of nonpalpable breast cancers present only as microcalcifications (6, 7). According to Elmore et al. (8), a mammography is able to detect approximately 90% of cancers in asymptomatic women up to 2 years before the cancers became symptomatic. It is well known that mammography is the most useful modality for detecting microcalcifications within the breast and it has been increasingly used worldwide for breast cancer screening. Because microcalcifications can also be observed in benign diseases of the breast such as fibrocystic disease, and a correlation is less specific in the detection of breast cancer (6).

To standardize the assessment and reporting of breast lesions identified on mammograms, ACR has developed the BI-RADS. The lexicon provides recommendations for action to be taken, facilitates research, and quality assessment by follow-up study of the final assessment categories (1, 9).

Because the coarse heterogeneous descriptor was only introduced in 2003, relatively few studies have been performed analyzing its predictive power. Burnside et al. (3) reported a positive predictive value of CHCs as 7% and Bent et al. (10) reported that 20%. Bent et al. (10) proposed that CHC in a clustered, linear, ductal, or segmental distribution should be classified as intermediate suspicion of malignancy (positive predictive value 36%). However, there has been no study dedicated to CHCs as far as we know. Compared with these previous results, the risk of malignancy in our study is relatively high 52% among the 27 pathologically proven lesions (14/27). In our results, 57% of the cases were DCIS, whereas the other 36% represented invasive carcinoma. The frequency of DCIS is similar to previously reported findings.

Although microcalcification distribution descriptors are not divided into specific risk categories in the BI-RADS (2), it has been suggested that the use of combined descriptions (morphology and distribution) may improve the predictability of mammography (3). Also, it is known that progression or stability of microcalcifications in the number or morphology on follow up is important.

Tanaka et al. (11) suggested that benign calcifications within a breast mass are not diagnostic of a benign process if the imaging characteristics of the mass are suspicious. In our study, we examined the clinical data with respect to the likelihood of malignancy in biopsies from CHCs on breast mammograms. We found a relatively high percentage (52%) of malignancy in such lesions. We evaluated whether the distribution of microcalcification, the presence of accompanying mass and its size on mammography help predicting the risk of malignancy and the histopathological results correlated with the mammographic findings in all cases.

Taken broadly, our result fits with the suggestion by Bent et al. (10) that CHCs in a clustered, linear, ductal or segmental distribution should be classified as BI-RADS 4b. However, our results further emphasize that special attention is needed when interpreting CHCs with a segmental distribution which in our study which showed a significant relationship to malignant rather than benign lesions ($p < 0.05$). The size of the CHC area correlated with the possibility of malignancy in our study. The area of malignant CHCs had a significantly larger diameter than that of benign lesions ($p < 0.05$). On mammography, masses were accompanied with both benign and malignant types of CHCs, while the presence of mass and its size were not a statistically significant predictor of malignancy. However, further evaluation with a larger patient population is needed to confirm its clinical value, considering the intermediate significance (p-value of 0.385 and 0.095).

There are some limitations to our study; first, is its retrospective nature. Second, from a practical point of view, pure CHC morphology was not common and many cases showed a mixed pattern of morphology. Because we selected cases with predominantly CHCs, a relatively small sized study group was available. Cases without pathological confirmation were excluded in our study and only 27 patients with radiologic-pathologic correlation were included. The overall malignancy rate is relatively high (52%) in this study, largely because of the above mentioned reasons. Third, we did not account for inter-observer variability in our study design, even though the radiologic findings were reviewed by only two experienced breast

radiologists. It is well known that there are considerable inconsistencies in agreement between observers in the classification of microcalcification descriptors in BI-RADS usage (12). It would be valuable to further evaluate such information in a prospective way with a larger number of patients and with a correction for inter-observer variability.

In conclusion, the probability of malignancy was 52% in CHC lesions from our study. Results of our work demonstrate that the segmental distribution of CHCs and larger size of CHC area on mammography can help further stratify the risk of malignancy with statistical significance ($p < 0.05$). Even though there is considerable overlap between the mammographic features of benign and malignant lesions, considering the distribution of the CHCs, their size and accompanying findings can contribute to decision-making in practice.

REFERENCES

1. American College of Radiology. *Breast imaging reporting and data system (BI-RADS)*. 3rd ed. Reston: American College of Radiology, 1998
2. American College of Radiology. *Breast imaging reporting and data system (BI-RADS)*. 4th ed. Reston: American College of Radiology, 2003
3. Burnside ES, Ochsner JE, Fowler KJ, Fine JP, Salkowski LR, Rubin DL, et al. Use of microcalcification descriptors in BI-RADS 4th edition to stratify risk of malignancy. *Radiology* 2007;242:388-395
4. Chan KKK, Lui CY, Chu T, Chan KK, Yan AT, Wong K, et al. Stratifying risk for malignancy using microcalcification descriptors from the Breast Imaging Reporting and Data System 4th edition: experience in a single centre in Hong Kong. *J HK Coll Radiol* 2009;11:149-153
5. Tse GM, Tan PH, Pang AL, Tang AP, Cheung HS. Calcification in breast lesions: pathologists' perspective. *J Clin Pathol* 2008;61:145-151
6. Feig SA, Galkin BM, Muir HD. Evaluation of breast microcalcifications by means of optically magnified tissue specimen radiographs. *Recent Results Cancer Res* 1987;105:111-123
7. Sickles EA. Mammographic features of 300 consecutive nonpalpable breast cancers. *AJR Am J Roentgenol* 1986;146:661-663
8. Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. *JAMA* 2005;293:1245-1256
9. D'Orsi CJ. The American College of Radiology mammography lexicon: an initial attempt to standardize terminology. *AJR Am J Roentgenol* 1996;166:779-780
10. 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;194:1378-1383
11. Tanaka K, Akiyama F, Nishikawa N, Kimura K, Gomi N, Oda K, et al. Invasive carcinoma of the breast accompanied by coarse calcification. *AJR Am J Roentgenol* 2009;193:W70-W71
12. Baker JA, Kornguth PJ, Floyd CE Jr. Breast imaging reporting and data system standardized mammography lexicon: observer variability in lesion description. *AJR Am J Roentgenol* 1996;166:773-778

유방촬영술에서 발견된 거친 비균질성 석회화의 임상적 의의와 병리 소견의 고찰[1]

임현주[1] · 조규란[1] · 서보경[1] · 우옥희[1] · 황규원[1] · 오유환[1] · 배정원[2] · 박경화[3]

목적: 유방촬영술에서 발견된 거친 비균질성 석회화의 임상적 중요성과 병리 소견을 알아보고자 하였다.

대상과 방법: 2006년 1월부터 2010년 8월까지 본원에서 시행된 유방촬영술에서 발견된 거친 비균질성 석회화를 가진 65명의 여성들 중에서 병리적으로 확진된 27명(양성 13명, 악성 14명)의 환자를 대상으로 하였다. 유방촬영술에서 거친 비균질성 석회화의 분포(군집성, 선상, 구역성, 국소성, 미만성)와 범위, 동반된 종괴의 유무 및 크기 등을 두 명의 유방영상의학과 의사가 합의하에 후향적으로 분석하였다. 유방초음파 검사를 시행한 26명의 경우, 종괴의 유무, 유관의 변화, 유방실질 에코의 변화 등을 분석하였다. 또한, 악성을 예측할 수 있는 영상소견이 있는지 알아보았다.

결과: 거친 비균질성 석회화의 분포의 경우, 전체 22예의 군집성 분포 중 8예, 2예의 선상 분포 중 1예, 5예의 구역성 분포 중 5예가 악성을 나타냈으며, 구역성 분포는 통계학적으로 유의한 결과를 보였다($p < 0.05$). 악성으로 판명된 거친 비균질성 석회화의 범위는 양성의 경우보다 통계적으로 유의하게 넓었다($p < 0.05$). 유방촬영술에서 거친 비균질 석회화에 동반된 종괴는 양성인 13경우 중 2예에서, 악성인 14경우 중 5예에서 확인되었다. 하지만 유방촬영술상 동반된 종괴의 여부나 그 크기는 유의한 악성 예측률을 나타내지 않았다. 유방초음파소견 역시 양성과 악성 간에 유의한 차이를 보이지 않았다.

결론: 유방촬영술에서 발견된 거친 비균질성 석회화는 52%에서 악성과 연관이 있었으며(14/27), 구역성 분포를 보이고 석회화의 범위가 크면 악성일 가능성이 높았다.

고려대학교 의과대학 [1]영상의학과, [2]외과, [3]종양내과