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Screening mammography-detected ductal carcinoma in situ: mammographic features based on breast cancer subtypes

Mi Young Kim [a], Hyeon Sook Kim [b,*], Nami Choi [a], Jung-Hyun Yang [c], Young Bum Yoo [c], Kyoung Sik Park [c]

[a] Department of Radiology, Konkuk University Medical Center, Konkuk University School of Medicine
[b] Department of Radiology, St.Paul's Hospital, Catholic University of Korea
[c] Department of Surgery, Konkuk University Medical Center, Konkuk University School of Medicine

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ABSTRACT

We evaluated the mammographic and histopathologic features of screening mammography-detected ductal carcinoma in situ (DCIS) based on the breast cancer subtypes determined by immunohistochemistry. A total of 94 patients with 94 screening mammography-detected DCIS were included in this study. Mammographically, human epidermal growth factor receptor 2 (HER2)-positive DCIS was more commonly associated with calcifications than estrogen receptor (ER)-positive and triple-negative DCIS ($P = .003$). Histopathologically, HER2-positive DCIS and triple-negative DCIS were associated with high nuclear grade ($P \leq .001$) and comedo necrosis ($P \leq .001$) than ER-positive DCIS.

1. Introduction

Ductal carcinoma in situ (DCIS) of the breast is due to the proliferation of malignant-appearing epithelial cells without stromal invasion and is a rare condition that only accounted for 0.8–5% of all breast cancers before the widespread use of screening mammography [1]. In recent years, the frequency of DCIS detection has greatly increased due to mammographic screening in asymptomatic women, and this diagnosis is now made in approximately 30% of breast cancers in the screening population [2–4]. Screening mammography enabled early detection of DCIS before it progresses to invasive breast cancer. Mammography primarily identifies microcalcifications that are commonly associated with DCIS and is highly sensitive.

Many researchers have reported that molecular profiling is significantly associated with biologic features of invasive breast cancers, and a significant difference exists in prognosis as well as the response to local and systemic therapy according to molecular subtypes [5–9]. The biological subtypes that can be approximated with immunohistochemical evaluation of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression are roughly correlated with the molecular subtypes of luminal, HER2 enriched, and basal like by gene expression profiling [10]. In patients with surgically treated DCIS, negative ER and positive HER2 status are significantly associated with a risk of local recurrence [11,12]. In terms of histopathologic features, high nuclear grade and comedo necrosis are associated with a higher risk of local recurrence in patients with DCIS [13–17].

Early detection and management of DCIS is very important because DCIS is a precursor of invasive breast cancer, which can be potentially lethal [2]. Mammography is a valuable diagnostic modality for detection of DCIS, and mammographic calcifications are known to be dominant imaging features of DCIS [18,19]. Mun et al. reported that PR positivity and HER2 positivity are significantly associated with mammographic calcifications in patients with DCIS [20]. Bae et al. demonstrated that a significant difference exists in morphology and distribution of the calcifications in patients with DCIS that presented as mammographic calcifications according to breast cancer subtypes [21].

However, little description is found in the literature regarding the mammographic features of screening mammography-detected DCIS based on breast cancer subtypes determined by immunohistochemistry.

The purpose of this retrospective study was to evaluate the mammographic features of screening mammography-detected DCIS based on the breast cancer subtypes determined by immunohistochemistry and to investigate histopathologic features based on the presence of mammographic calcifications.

2. Material and methods

2.1. Study population and clinicopathologic data

The institutional review board approved this retrospective study protocol, and a waiver of informed consent was obtained. We searched the surgical pathology database and identified 220 patients who were diagnosed with DCIS from 2007 to 2013. Patients with DCIS associated

* Corresponding author. Department of Radiology, St.Paul's Hospital, Jeonnong 1-dong, Dongdaemun-gu, Seoul, 130-709, Korea. Tel.: +82-2-958-2084; fax: +82-2-961-4552.
E-mail address: hskimsph@catholic.ac.kr (H.S. Kim).

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with minimal invasion or axillary involvement were not included in the study. Among the 220 patients, 132 (60.0 %) with 137 cases were categorized as having screening mammography-detected DCIS. Of these, 43 cases were excluded because there were no immunohistochemical evaluations. Finally, 94 patients (mean age, 53.8±8.8 years; range, 26–74 years) with 94 screening mammography-detected DCIS were included in our study population.

We reviewed and recorded each patient's clinical and pathological features to determine the tumor size, tumor grade, hormone receptor status (ER, PR, and HER2) and presence of nodal metastases. The ER, PR, and HER2 statuses were determined by immunohistochemical analysis. For the immunohistochemical analysis, formalin-fixed, paraffin-embedded tissue sections were immunohistochemically stained. The Allred score was used to determine the ER and PR statuses. The results were classified as positive when the total score, expressed as the sum of the proportion and immunointensity scores, was 3 or more. The intensity of the c-erbB-2 staining was scored as 0, 1+, 2+, or 3+. Tumors with a 3+ score were classified as HER2-positive, and tumors with a 0 or 1+ score were classified as negative. In tumors with a 2+ score, gene amplification using silver in situ hybridization was used to determine the HER2 status. The HER2 expression was considered positive if the ratio of HER2 gene copies to chromosome 17 signals was >2.

2.2. Mammography review

Digital mammography was performed using a Selenia system (Lorad, Bedford, CT, USA). Standard two-view mammography (mediolateral oblique and craniocaudal) was performed with additional views such as magnification or spot compression view as necessary. Two dedicated breast radiologists (_._._and_._._) with 6 and 20 years of experience retrospectively reviewed all mammograms in consensus without knowledge of the clinicopathological findings of the cases. Following mammography, lesion types were classified into the following four categories: negative, mass or asymmetry, calcifications, and mass or asymmetry with calcifications. If the lesion was associated with the calcifications, features of the calcifications were described in morphology and distribution according to the BI-RADS Lexicon [22]. Breast density was also rated as fatty, scattered fibroglandular, heterogeneously dense, or extremely dense according to the BI-RADS Lexicon.

2.3. Statistical analysis

The clinicopathological and mammographic features were compared between the ER-positive, HER2-positive, and triple-negative DCIS using the chi-square or Fisher's Exact Tests for categorical variables and analysis of variance or the Kruskal–Wallis test for continuous variables. The clinicopathologic features were also compared between calcified and noncalcified DCIS using the chi-square or Fisher's Exact Tests for categorical variables and Student's *t* test or the Mann–Whitney *U* test for continuous variables. All statistical analyses were carried out using SPSS version 17.0 for Windows (SPSS, Chicago, IL, USA). The results were considered significant at *P*-values <.05.

3. Results

Out of the 94 screening mammography-detected DCIS, 49 (52.1%) were ER-positive DCIS, 40 (42.6%) were HER2-positive DCIS, and 5 (5.3%) were triple-negative DCIS. Of the 40 HER2-positive DCIS, 22 were ER-negative, and 18 were ER-positive.

Table 1 lists the clinicopathological features of patients with screening mammography-detected DCIS based on the breast cancer subtypes. The mean ages of patients with ER-positive, HER2-positive, and triple-negative DCIS were 51.9, 52.9 and 53.8 years, respectively (*P*=.847). The mean tumor sizes were 2.2 cm, 3.3 cm, and 1.5 cm for ER-positive, HER2-positive, and triple-negative DCIS, respectively (*P*=.028). The nuclear grade and presence of comedo necrosis were significantly different across the subtypes. A significantly higher percentage of nuclear Grade 3 was observed in HER2-positive DCIS (62.5%, 25 of 40) and triple-negative DCIS (60.0%, 3 of 5) than in ER-positive DCIS (8.2%, 4 of 49) (*P*≤.001). HER2-positive DCIS and triple-negative DCIS were more likely to be associated with comedo necrosis than ER-positive DCIS (*P*≤.001).

Table 1
Clinicopathological features of 94 screening mammography-detected DCIS based on breast cancer subtypes

Clinicopathological features	ER-positive (*n*=49)	HER2-positive (*n*=40)	Triple negative (*n*=5)	*P* value
Mean age (years)	51.9±9.9	52.9±9.4	53.8±5.2	.847
Mean tumor size (cm)	2.2±2.0	3.3±2.3	1.5±0.6	.028
Nuclear grade				<.001
Grade1	8 (16.3)	0 (0.0)	0 (0.0)	
Grade2	37 (75.5)	15 (37.5)	2 (40.0)	
Grade3	4 (8.2)	25 (62.5)	3 (60.0)	
Comedo necrosis				<.001
No	28 (57.1)	4 (10.0)	0 (0.0)	
Yes	21(42.9)	36 (90.0)	5 (100.0)	

Note: Percentages are in parentheses.

Mammographically, the lesion type of screening mammography-detected DCIS was significantly different between the subtypes (*P*=.009) (Table 2). Mammograms of 49 ER-positive DCIS showed 14 (28.6%) asymmetries or masses, 32 (65.3%) calcifications, and 3 (6.1%) asymmetries or masses with associated calcifications. Mammograms of 40 HER2-positive DCIS showed 1 (2.5%) asymmetry, 31 (77.5%) calcifications, and 8 (20.0%) asymmetries or masses with associated calcifications. Mammograms of 5 triple-negative DCIS showed 3 (60.0%) calcifications and 2 asymmetries or masses (40.0%). In total, calcifications were associated in 71.4% of ER-positive DCIS, 97.5% of HER2-positive DCIS, and 60.0% of triple-negative DCIS (*P*=.003) (Fig. 1).

With regard to the morphologic feature of calcifications, there was no significant difference between the subtypes (*P*=.869). Out of 49 ER-positive DCIS, 35 (71.4%) were associated with calcifications: fine pleomorphic in 18 (51.4%), amorphous in 9 (25.7%), fine linear or linear branching in 5 (14.3%), and the other in 3 (8.6%). Out of 40 HER2-positive DCIS, 39 (97.5%) were associated with calcifications: fine

Table 2
Mammographic features of 94 screening mammography-detected DCIS based on breast cancer subtypes

Mammographic features	ER-positive (*n*=49)	HER2-positive (*n*=40)	Triple-negative (*n*=5)	*P* value
Lesion type				.006
Mass or asymmetry	14 (28.6)	1 (2.5)	2 (40.0)	
Calcifications	32 (65.3)	31 (77.5)	3 (60.0)	
Mass or asymmetry with calcifications	3 (6.1)	8 (20.0)	0 (0.0)	
Presence of calcifications	35 (71.4)	39 (97.5)	3 (60.0)	.003
Morphology of calcifications				.869
Punctate	1 (2.9)	3 (7.7)	0 (0.0)	
Amorphous	9 (25.7)	6 (15.4)	1 (33.3)	
Coarse heterogenous	2 (5.7)	1 (2.6)	0 (0.0)	
Fine pleomorphic	18 (51.4)	23 (59.0)	1 (33.3)	
Fine linear or linear branching	5 (14.3)	6 (15.4)	1 (33.3)	
Distribution of calcifications				.564
Regional	7 (20.0)	4 (10.3)	0 (0.0)	
Clustered	15 (42.9)	22 (56.4)	3 (100.0)	
Linear	3 (8.6)	3 (7.7)	0 (0.0)	
Segmental	10 (28.6)	10 (25.6)	0 (0.0)	
Breast density				.444
Almost fat	0 (0.0)	0 (0.0)	0 (0.0)	
Scattered fibroglandular	14 (28.6)	7 (17.5)	0 (0.0)	
Heterogenously dense	27 (55.1)	28 (70.0)	4 (80.0)	
Extremely dense	8 (16.3)	5 (12.5)	1 (20.0)	

Note: Percentages are in parentheses.