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Calcified and Non-Calcified Ductal Carcinoma *in Situ*: Contrast-Enhanced MRI Features and Pathological Correlation

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Abstract

Background: Early detection of ductal carcinoma *in situ* (DCIS) is essential for improving the prognosis of breast cancer. Among mammographically detected DCIS cases, approximately 10% - 20% of DCIS cases are manifested as non-calcified. **Purpose:** To evaluate differences in MRI findings and histological features between mammographically evident non-calcified and calcified DCIS. **Material and Methods:** This study included 84 cases of pathologically proven DCIS in 82 patients who underwent preoperative breast MRI. The lesions were divided into non-calcified and calcified DCIS according to the presence of calcifications on mammography. MRI features were analyzed according to the enhancement pattern. The pathologic features were also reviewed. **Results:** Among the 84 DCIS cases, 30 (36%) were classified as non-calcified DCIS, and 54 (64%) as calcified DCIS on mammography. On MRI, 27% (8/30) of non-calcified DCIS and 17% (9/54) calcified DCIS presented as mass enhancement, 73% (22/30) non-calcified DCIS and 83% (45/54) calcified DCIS presented as non-mass enhancements. No significant difference in the type of lesion was observed between non-calcified and calcified DCIS ($p = 0.274$). Histopathologically, high nuclear grade, presence of necrosis, and presence of HER-2 status were more common in calcified DCIS than in non-calcified DCIS ($p < 0.05$). **Conclusion:** There were no significant differences in MRI findings between non-calcified and calcified DCIS. However, calcified DCIS had more aggressive histological features than non-calcified DCIS.

Keywords

Ductal Carcinoma *in Situ*, Mammography, Microcalcification, Magnetic Resonance Imaging

1. Introduction

Ductal carcinoma *in situ* (DCIS) is a breast malignancy characterized pathologically by proliferation of malignant ductal epithelial cells in the lining of the terminal duct lobular unit without invasion through the basement membrane [1]. In recent years, the widespread use of mammographic screening has been chanced on DCIS more frequently. DCIS now accounts for as many as 30% of breast cancers in screened populations, and for approximately 5% of breast carcinomas in symptomatic women [2] [3]. DCIS comprises a spectrum of noninvasive malignant processes in the breast with the potential to develop into an invasive cancer, and in fact approximately 30% - 50% of DCIS cases do progress to invasive breast cancer [4] [5]. Therefore, early detection of DCIS is essential for improving the prognosis of breast cancer.

Among mammographically detected DCIS cases, up to 79% manifest with microcalcifications [3], typically with a coarse, heterogeneous, or fine pleomorphic morphology, distributed in clusters, or in a segmental and linear-branching pattern [6]. However, approximately 10% - 20% of DCIS cases are manifested as non-calcified lesions on mammography, such as masses, architectural distortion, dilated retro areolar ducts, and developing densities. In addition, 16% of DCIS lesions are reported to be occult on mammography [3] [7] [8].

On magnetic resonance imaging (MRI), DCIS exhibits various features, such as a mass with a washed-out or plateau pattern upon kinetic analysis or as non-mass enhancement. With the development of higher spatial resolution techniques, MRI has become to detect significantly more cases of any grade of DCIS than mammography [9] [10]. To our knowledge, there is very little literature describing the MR imaging features of mammographically evident non-calcified DCIS, and few studies have correlated histopathological features with non-calcified DCIS [4] [11].

Therefore, the purpose of the present study was to compare the MRI and histopathological features between mammographically non-calcified DCIS and calcified DCIS.

2. Material and Methods

2.1. Patients

Our institutional review board approved the study protocol. The research ethics board did not require approval for this retrospective review of images and data.

Using a computer database system, we searched for and recruited patients who had undergone surgical treatment of primary breast cancers at our institution between January 2011 and December 2014. A total of 109 consecutive patients with pathologically diagnosed pure DCIS based on the final pathological reports were included. All patients consented to modified mastectomy or partial resection of the breast. DCIS associated with minimal invasion and accompanied by invasive cancers were not included. We excluded 27 cases due to absence of MRI data. Two patients had bilateral DCIS. Thus, a final total of 84 DCIS cases

in 82 patients (age 24 - 83 years; mean 53 years) were included.

2.2. Mammography

Mammography was performed using either Senographe DS (GE Healthcare, USA) or MAMMOMAT Inspiration (Siemens, Germany). Patients underwent cranio-caudal and medio-lateral oblique views ± lateral and magnified and spot compression views as medically necessary.

2.3. MRI

All MRI imaging was undertaken on a 3.0T scanner (Achieva Philips Healthcare Best, Netherlands) in conjunction with an 8-channel phased-array breast surface coil.

For MRI, an axial fat-suppressed fast spin-echo T2-weighted image was obtained, and dynamic contrast-enhanced T1-weighted fat-saturated gradient-echo sequences were performed before and four times after a bolus injection of gadolinium (Magnevist, Bayer Yakuhin, Japan) at a dose of 0.1 mmol per kilogram body weight, followed by flush-out with 20 ml of saline solution. After unenhanced acquisition, the first contrasted acquisition was performed 20 seconds after injection, and the last acquisition was performed over a period of 6 minutes after injection. Standard subtraction images were created from the non-enhanced and early and late contrast-enhanced T1-weighted fat-saturated gradient-echo sequences.

2.4. Image Interpretation

All images were retrospectively evaluated by two breast radiologists with 15 and 7 years of clinical experience. They were blinded to other information and evaluated the lesion morphology independently. Discordances were discussed until a consensus was reached.

Mammographic characteristics were evaluated according to the Breast Imaging Reporting and Data System (BI-RADS) [12]. Lesions were classified as belonging to five categories: 1) negative, 2) calcifications alone, 3) mass with calcifications, 4) mass without calcifications, 5) other findings. The "other findings" category included focal asymmetric density and architectural distortion.

Using MR images, morphological analysis was performed in consensus according to the BI-RADS MRI lexicon [12]. The enhancement pattern on MRI was analyzed by qualitative assessment of contrast uptake in the initial phase (first 2 min) and the delayed phase, which in turn was defined by the BI-RADS MRI lexicon to comprise the persistent, plateau, and washout phases [12].

2.5. Histopathology

Participant's histopathological details were obtained from the electronic patient notes system. The following histological parameters were analyzed: nuclear grade (modified Bloom and Richardson grading; 1) low grade, 2) intermediate,

or 3) high), the presence of necrosis, estrogen receptor (ER) status, progesterone receptor (PR) status, HER-2 status and tumor size. HER-2 status was initially determined by immune histochemical staining (IHC), and was scored as positive in tumors with a 3+ staining score and negative in tumors with scores of 0 and 1+. Tumors scored as IHC 2+ were further evaluated by fluorescence *in situ* hybridization (FISH). Tumors were considered positive for ER and PR when strong nuclear staining was observed in at least 10% of the tumor cells tested.

2.6. Statistical Analysis

Statistical analysis was performed using a statistical software package (SPSS, version 21.0, SPSS, Chicago, IL, USA). Inter-observer agreement was evaluated by kappa test. Kappa values higher than 0.75 were considered to indicate excellent agreement. For differences in the imaging and histopathological features between the two groups, the chi-squared test and Fisher's exact test were employed. A p value of 0.05 or lower was considered significant.

3. Results

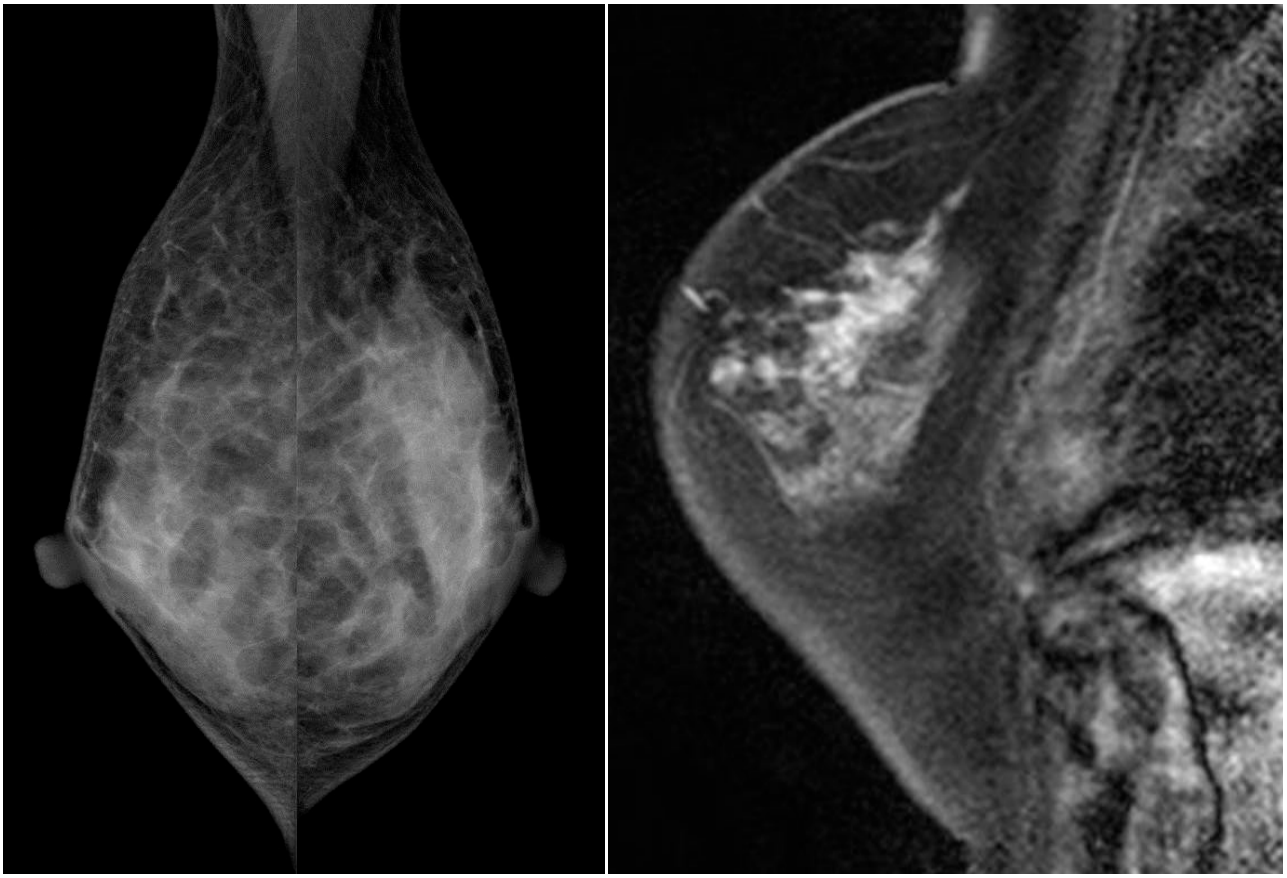
Inter-observer agreement between the two radiologists was excellent, with a kappa value of 0.925 for evaluation of mammographic characteristics, and 0.854 for morphological analysis of MR images.

Among the 84 DCIS lesions, 30 (36%) in 30 women (age 24 - 83 years; mean 55 years) were defined as non-calcified DCIS, and 54 (64%) in 52 women (aged 35 - 79 years; mean 52 years) were defined as calcified DCIS. Patients with non-calcified DCIS did not significantly differ from patients with calcified DCIS in terms of mean age ($p = 0.375$). A palpable mass was found in 16 (53%) cases in the non-calcified DCIS group and in 17 (31%) in the calcified DCIS group.

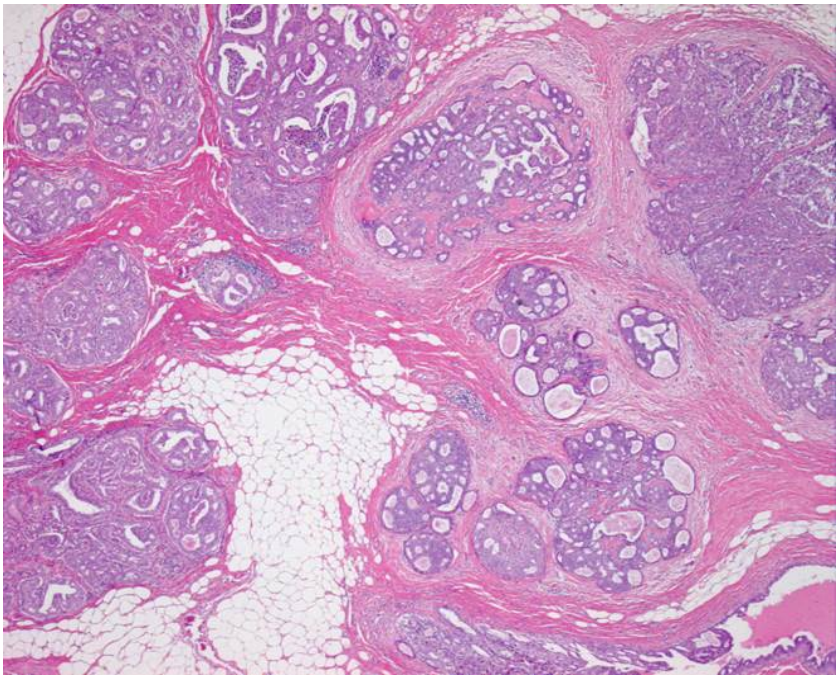
3.1. Mammography

The overall sensitivity of mammography for DCIS was 92% (77/84). Regarding the non-calcified DCIS group, which included 30 cases, mammography was falsely negative in 7 cases (23%) (**Figure 1**), detected masses in 8 (27%) (**Figure 2**), focal asymmetric density in 10 (33%), and architectural distortion in 5 (17%) (**Table 1**). Among the 8 mass lesions, the shape was round/oval in 6 (75%) and irregular in 2 (25%). The mass margins were circumscribed in 1 case (12.5%), microlobulated in 2 (25%), obscure in 4 (50%), and indistinct in 1 (12.5%). Of the 7 mammographically occult cases, 6 were located in dense breast parenchyma.

Regarding the calcified DCIS group, which included 54 cases, mammography detected calcification alone in 45 cases (83%) and masses with calcification in 9 cases (17%). The dominant morphologies of the calcifications were amorphous in 14 cases (26%), coarse heterogeneous in 17 (31.5%), fine pleomorphic in 17 (31.5%), and fine linear in 6 (11%). The distributions of the calcifications were diffuse in 1 case (2%), regional in 1 (2%), clustered in 2 (54%), segmental in 17 (31%), and linear in 6 (11%).

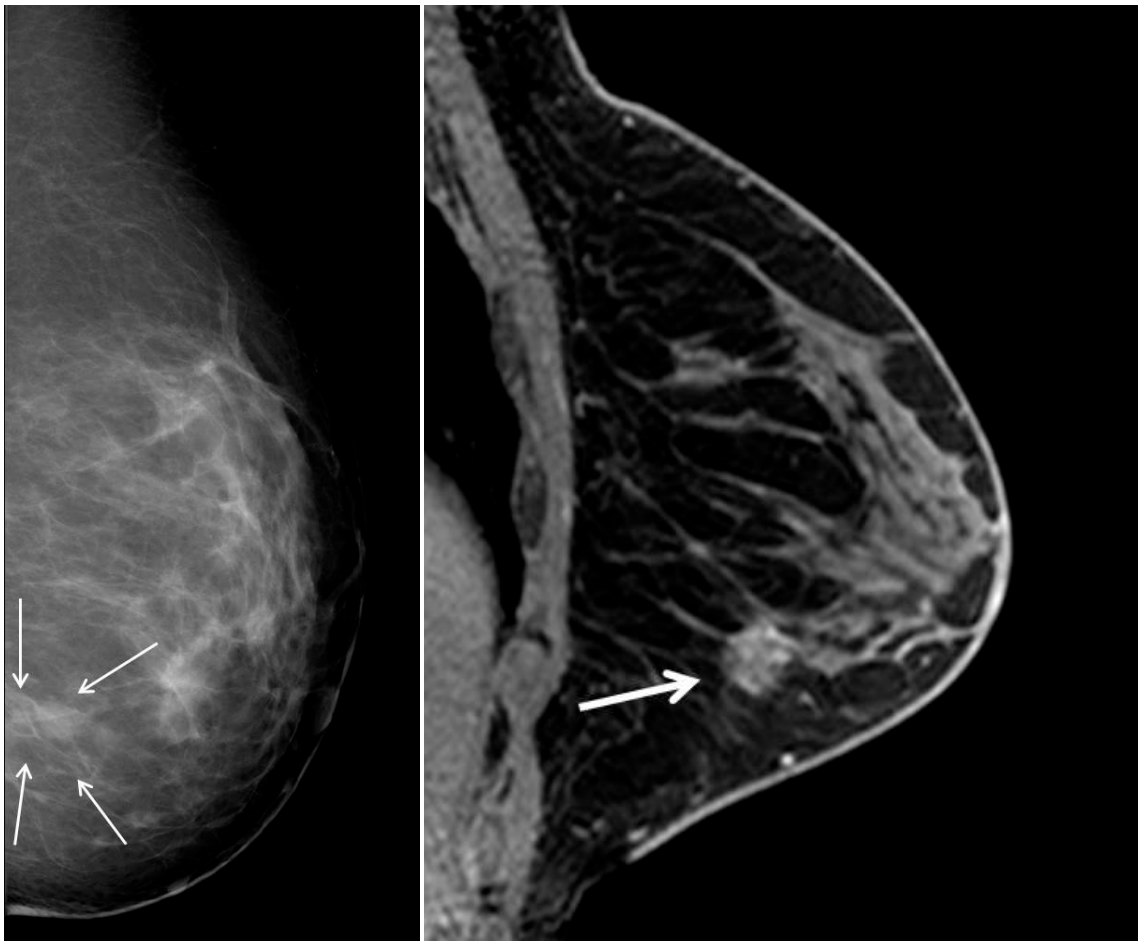


(a) (b)

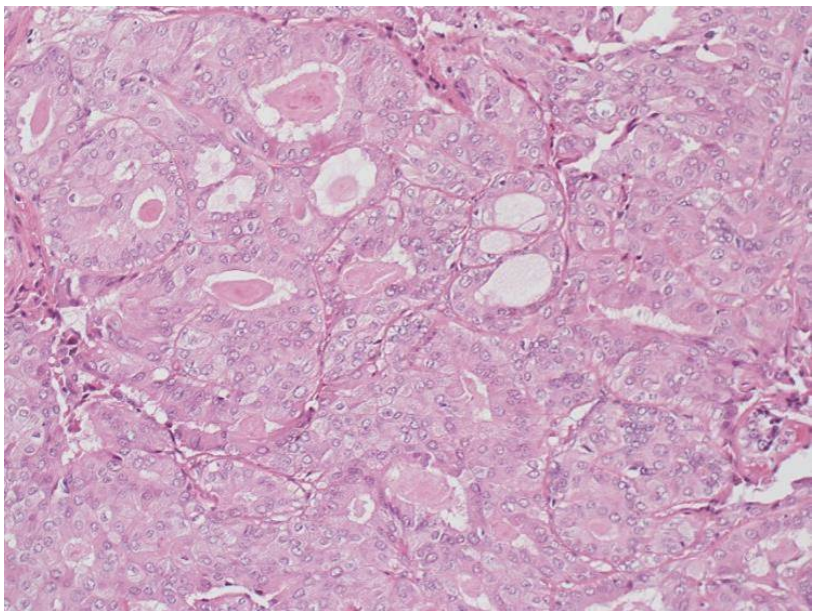


(c)

Figure 1. A 46-year-old woman with mammographically non-calcified DCIS. (a) Mammogram revealed negative finding. (b) MRI demonstrated non-mass enhancement in the upper inner portion of the left breast. (c) Final pathology result revealed a 55 mm ductal carcinoma *in situ*, cribriform and papillary type.



(a) (b)



(c)

Figure 2. A 50-year-old woman with mammographically non-calcified DCIS. (a) Left mammogram revealed a 10 mm irregular mass in the lateral aspect of the breast. (b) MRI demonstrated a mass with irregular internal enhancement. (c) Final pathology result revealed a 10 mm ductal carcinoma *in situ*, cribriform type.

3.2. MRI

MRI demonstrated a mass in 17 of the 84 cases (20%), and non-mass enhancement in 67 (80%) (Table 2). No significant difference in the type of the lesion

Table 1. Comparison of lesion types on mammography between non-calcified and calcified ductal carcinoma *in situ* (DCIS).

Mammography feature	Non-calcified DCIS	Calcified DCIS
	30	54
Calcification alone		45 (83)
Mass with calcification		9 (17)
Mass without calcification	8 (27)	
Focal asymmetric density	10 (33)	
Architectural distortion	5 (17)	
False-negative	7 (23)	

Data are numbers of cases. Numbers in parentheses are percentages.

Table 2. Comparison of magnetic resonance imaging (MRI) features between non-calcified and calcified ductal carcinoma *in situ* (DCIS).

MRI feature	Non-calcified DCIS	Calcified DCIS	p-Value
Mass	8	9	
Shape			0.2668
Oval	2 (25)	0 (0)	
Round	1 (12)	1 (11)	
Irregular	5 (63)	8 (89)	
Margin			0.0824
Circumscribed	0 (0)	0 (0)	
Irregular	5 (63)	9 (100)	
Spiculated	3 (37)	0 (0)	
Internal enhancement			0.0978
Homogeneous	0	1 (11)	
Heterogeneous	5 (63)	8 (89)	
Rim enhancement	3 (37)	0	
Non-mass enhancement	22	45	
Distribution			0.1255
Focal area	2 (9)	9 (20)	
Linear	6 (27)	4 (9)	
Segmental	12 (55)	31 (69)	
Regional	1 (4.5)	0 (0)	
Diffuse	1 (4.5)	1 (2)	
Internal enhancement			0.6469
Homogeneous	0 (0)	0 (0)	
Heterogeneous	7 (35)	13 (36)	
Clumped	9 (45)	19 (53)	
Clustered ring	4 (20)	4 (11)	

Data are numbers of cases. Numbers in parentheses are percentages.

was observed between the non-calcified and calcified groups (p = 0.274). Eight of the 30 (27%) cases of non-calcified DCIS and 9 of the 54 (17%) cases of calcified DCIS presented as a mass. There were no significant differences in terms of their shapes (p = 0.267), margins (p = 0.082), or enhancement patterns (p = 0.097). Twenty-two (73%) of the non-calcified DCIS cases and 45 of the 54 (83%) calcified DCIS cases presented as non-mass enhancement. The difference in distribution (p = 0.126) and internal enhancement (p = 0.647) between two groups was not significantly different.

3.3. Histopathology

The mean lesion diameter in the non-calcified DCIS group was 30.2 mm (range 5 - 75 mm) where as that in the calcified DCIS group was 33.2 mm (range 5 - 118 mm). The difference was not significant. The pathological results revealed more cases of a high nuclear grade (p = 0.018), presence of necrosis (p < 0.001), and presence of HER-2 status (p = 0.018) in the calcified DCIS group than in the non-calcified DCIS group. However, there were no significant inter-group differences in terms of the presence of ER (p = 0.679) or PR status (p = 0.101) (Table 3).

4. Discussion

The incidence of DCIS has been rising steadily. Currently, screening mammography is the most useful imaging modality for detection of DCIS. Microcalcification

Table 3. Comparison of histopathological features between non-calcified and calcified ductal carcinoma *in situ* (DCIS).

Histopathological feature	Non-calcified DCIS	Calcified DCIS	p-Value
Nuclear grade			0.018*
1	27	33	
2	2	17	
3	1	4	
Necrosis			<0.001*
Yes	2	27	
No	28	27	
Estrogen receptor			0.679
Positive	25	43	
Negative	5	11	
progesterone receptor			0.101
Positive	25	36	
Negative	5	18	
Her 2			0.018*
Positive	3	18	
Negative	27	36	

Data are numbers of cases. Numbers in parentheses are percentages.

is one of the most important features of DCIS on mammography, but not all DCIS lesions are calcified. Calcium can deposit on both necrotic debris (necrotic calcification) and non-necrotic materials, such as secretory or mucinous materials (non-necrotic calcification) [13] [14]. The sensitivity of mammography for detection of non-calcified DCIS has been reported to be about 20%. DCIS may also manifest as a mass on mammography in 10% of cases and as architectural distortion in 7% - 13% [3] [15] [16]. In the present study, the sensitivity of mammography for detection of non-calcified DCIS was 77% (23/30). In a study of 909 consecutive DCIS patients, Barreau *et al.* reported that low-grade DCIS was manifested as a mass or an asymmetric density more frequently than high-grade DCIS [16]. The presence of microcalcifications, especially those with a branching or fine linear morphology, strongly increases the chance of HER-2 overexpression [17] [18]. Several studies have indicated that HER-2 overexpression is associated with a relatively worse prognosis and increased rates of recurrence than other cancers [19] [20]. Alternatively, poorly differentiated tumors more often show central necrosis and rapid growth, resulting in deposition of microcalcifications along the ductal structures, and therefore this feature could also be a reflection of the more aggressive nature of HER2-positive invasive cancers [17].

In the present study, 7 of the non-calcified DCIS cases could not be detected by mammography, and 6 of these 7 cases occurred in dense breast tissue. Previous studies have demonstrated that 6% - 23% of DCIS cases overall were mammographically occult [3] [7] [8]. The present 7 mammographically occult DCIS were detected on MRI and demonstrated non-mass enhancement. Therefore, MRI could be considered a useful modality for detection and diagnosis of non-calcified DCIS in patients found to have dense breast tissues on mammography. The periductal stroma associated with DCIS has a higher microvessel density than normal breast tissue [21]. Jansen *et al.* postulated that ductal basement membrane permeability is elevated in the presence of DCIS, due to protease secretion from cancer cells, leading to an accumulation of gadolinium within the duct at the site of DCIS [22]. Consequently, MRI can detect DCIS more accurately than mammography, since it may be able to demonstrate mammographically occult or non-calcified DCIS. Though MRI has been regarded as the most sensitive method for detection of breast cancer, classical morphological signs had a limited accuracy in smaller compared to larger lesions [23]. It is difficult to diagnose DCIS especially in small cases and sometimes impossible to distinguish DCIS from benign lesion or normal parenchyma. To improve diagnostic accuracy and detection of such DCIS cases, high spatial resolution and high contrast differentiation of tissues on MRI are needed. Parallel imaging and multichannel coils are likely to improve spatial resolution and during routine diagnosis [23]. In addition, results of some investigators argued that improved diagnostic accuracy is achieved with 3.0T MRI [24] [25] [26].

Several authors have analyzed the difference between MRI features and pa-

thologic grade of DCIS. The MRI appearance of DCIS depends primarily on the presence and extent of abnormal periductal or stromal vascularity [27]. Some previous studies reported that the type of morphologic enhancement was correlated with histological grade. A few studies reported that the rate of non-mass enhancement increased according to nuclear grade and pathological grade [10] [28] [29]. Jiang *et al.* reported that internal enhancement with clumping is significantly associated with histological grade and prognosis, while Facius *et al.* and Neubauer *et al.* reported that segmental granular pattern of enhancement is more likely shown in intermediate and high-grade DCIS [30] [31] [32]. Concerning time-intensity curves, Neubauer *et al.* reported that plateau or washout pattern is significantly shown in intermediate and high-grade DCIS [32]. On the other hand, some studies have reported no correlation between enhancement pattern and nuclear grade of DCIS [9] [33]. The relationship between MRI features and pathologic grade remains controversial.

In our investigation, non-mass enhancement was the most common MRI finding in both non-calcified and calcified DCIS and there were no significant differences in lesion type or morphological appearance on MRI between non-calcified and calcified DCIS. However, we also found that a high nuclear grade, presence of necrosis, and positive HER-2 status were significantly more common in calcified than in non-calcified DCIS, which means that calcified DCIS has more aggressive histological features than non-calcified DCIS. These observations suggested that MRI findings of calcified DCIS might have features in relation to histological aggressiveness. The number of patients enrolled in this study was too small to draw significant conclusions. Therefore, further studies will be needed to confirm the characteristic MRI features of non-calcified and calcified DCIS in a large population.

Histological nuclear grade and presence of comedo necrosis in DCIS are important prognostic features. ER, PR, and HER-2 status are common biological markers in breast cancer. Most DCIS lesions express ER, PR, or both. In general, non-comedo carcinomas more frequently show ER positivity [34] [35]. Regarding the role of HER-2 status, immunoreactivity for the HER-2 oncogene has been primarily associated with high-grade DCIS [36], which has several implications for future research relevant to clinical care [18].

The present study had several limitations. First, the size of the population, especially the total number of patients, was relatively small in relation to the various parameters evaluated. Second, the retrospective nature of the study probably led to selection bias resulting from a difference between the patient population and a true screening setting. The selected patients had known disease; each patient in the cohort had histologically proven DCIS. To improve diagnosis of DCIS, however, DCIS that remain undetected or missed clinically and by imaging studies should also be evaluated. Further follow-up imaging study includes normal breast examination, some of which could conceivably have DCIS, would be needed. Third, we did not follow up the patients analyzed. To clarify the prognostic significance of our analysis, follow-up of patients and multifactorial

survival analysis will be required.

5. Conclusion

There were no significant differences in MRI findings between non-calcified and calcified DCIS. Histopathologically, calcified DCIS has more aggressive histological features than non-calcified DCIS. Recognition of the imaging features of non-calcified DCIS might be helpful for improving the diagnosis of DCIS.

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