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*Original Article*

# Differences in pathologic characteristics between ductal carcinoma in situ (DCIS), DCIS with microinvasion and DCIS with invasive ductal carcinoma

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**Abstract:** In order to further our understanding of pathologic features in various ductal carcinoma in situ (DCIS) related breast ductal cancers, including DCIS, DCIS with microinvasion (DCIS-Mi) and DCIS with invasive ductal carcinoma (DCIS-IDC), a retrospective study including 453 cases of DCIS, 88 cases of DCIS-Mi, and 269 cases of DCIS-IDC was conducted. Statistical analysis showed significant pathological differences were found in DCIS, DCIS-Mi, and DCIS-IDC. Compared with DCIS, DCIS-IDC was significantly more associated with high nuclear grade, large tumor size, high Ki67 index, and lymph node metastasis (all $P<0.05$). Higher expression of steroid receptors was shown in DCIS-IDC than in DCIS (all $P<0.05$), but the status of HER2 between the two groups was similar ($P=0.269$). Compared with DCIS, DCIS-Mi was significantly more associated with high nuclear grade, large tumor size, comedonecrosis, absence of steroid receptors, HER2 overexpression, and high Ki67 index (all $P<0.05$). These features remain consistently even when compared with DCIS-IDC. According to the immunohistochemistry surrogate classification, the dominant types of DCIS and DCIS-IDC were luminal types (luminal A and luminal B, respectively), while the dominant type of DCIS-Mi was HER2 overexpression. These findings suggest that DCIS-Mi represents a distinct entity, and DCIS with features including high nuclear grade, large tumor size, comedonecrosis, steroid receptors negativity, HER2 positivity, and high Ki67 expression was more likely to have microinvasion than DCIS without these features.

**Keywords:** ER, PR, HER2, DCIS, IDC, microinvasion

## Introduction

Ductal carcinoma in situ (DCIS) is defined as mammary carcinoma that has not yet broken through the ductal basement membrane and accounts for 20% of newly diagnosed breast cancers [1]. As a noninvasive lesion, it is considered to be the obligate precursor of invasive ductal carcinoma (IDC) [2, 3]. Approximately 14%-53% of untreated DCIS cases will naturally progress to IDC [4]. It is valuable to identify features of subpopulations with malignant potential for the management of this varied disease.

DCIS with microinvasion (DCIS-Mi) is DCIS that is no longer in situ but has one or more microscopic invasive foci not exceeding 1 mm in the longest diameter [5], and accounts for 10%~20% of DCIS and 1% of breast cancers [6]. Some scholars believe that DCIS-Mi is the interim stage in the progression from DCIS to IDC [7, 8]. Identifying changes between them will be helpful for finding associated instances of microinvasion and further understanding the progression of breast cancer [9].

Pathologic indexes, such as nuclear grade, tumor size, steroid receptor status (ER and PR), HER2 status, Ki67 level, etc., are commonly used for evaluating breast cancer and are associated with the progress, management, and prognosis of breast cancer. However, their differences in various stages of DCIS-related

breast ductal cancer (including DCIS, DCIS-Mi, and DCIS-IDC) are still unclear, and some of them are controversial [10, 11]. Therefore, our aim was to further our understanding of pathologic features in various DCIS-related breast ductal cancers, compare differences between them, and identify the potential risk factors for coexisting microinvasion in DCIS.

## Materials and methods

In total, 810 slides of 801 cases with mammary ductal carcinoma were reviewed at Qilu Hospital of Shandong University from January 1, 2008, to December 31, 2017 (Ethics Committee approval number KYLL-2018-096), including 453 slides of DCIS, 88 slides of DCIS-Mi, and 269 slides of DCIS-IDC. Pathologic data were obtained by reviewing archival medical records, including patient sex and age, tumor nuclear grade, tumor size, presence of comedonecrosis, multifocality of the lesion, lymph node status, and immunohistochemistry (IHC) results (including estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki67). The IHC results of DCIS-Mi were derived from the intraductal component because of the limited invasive lesion. In the case of DCIS-IDC, the IHC results of the invasive component alone were recorded if the two components (invasion and noninvasion) were not recorded separately.

Estrogen and progesterone receptors were considered to be positive as long as 1% of the tumor nuclei exhibited staining. HER2 expression was classified into 4 grades according to the ASCO/CAP 2013 guidelines [12], in which 0/1+ was considered to be negative, 2+ was indeterminate, and 3+ was positive. Fluorescence in situ hybridization was not performed. Ki67 was considered to be high if 14% or more of the tumor cells showed positive staining, as the 2013 St. Gallen guidelines recommended [13]. Four IHC indexes were analyzed using rabbit monoclonal antibodies from Ventana (Tucson, AZ, USA): ER (SP1), PR (1E2), HER2 (4B5), and Ki67 (30-9). Microinvasion was defined as the diameter of the infiltrating focus with DCIS not exceeding 1 mm, and stage T1a-b referred to the subpopulation of DCIS-IDC cases with a long diameter of 1 mm to 10 mm as recommended by the UICC/AJCC TNM classification.

Cases were classified into four subtypes according to the 2011 St. Gallen guidelines using IHC results as a surrogate to define the classification [14]: luminal A (ER+ and/or PR+, HER2-, and Ki67 <14%), luminal B (ER+ and/or PR+, HER2-, and Ki67 ≥14%: defined as luminal B HER2- subtype; and ER+ and/or PR+ and HER2+: defined as luminal B HER2+ subtype), HER2 overexpression (ER-, PR-, HER2+), and basal-like (ER-, PR-, HER2-).

Data were examined using SPSS 22.0 software. Differences were analyzed with Pearson's chi-squared test, the Kruskal-Wallis test, and the Mann-Whitney U test according to different variable properties. The McNemar test was used to test the matched data consistency. Statistical significance was set at $P<0.05$, and the Bonferroni adjusted *P* value was used for comparisons between three groups with the chi-square test.

## Results

### *Pathologic findings*

The pathologic characteristics of 810 slides of 801 cases with breast ductal carcinoma in various stages are shown in **Table 1**. There was no significant difference in sex, age or side among the three groups (P=0.626, P=0.374, and P=0.994, respectively). The proportions of high nuclear grade were 40.2% in DCIS, 77.6% in DCIS-Mi, and 61.6% in DCIS-IDC. Significant differences were found among them by the Kruskal-Wallis test (P=0.000) and between any two groups by the Mann-Whitney U test (all $P<0.05$). The average diameters were 2.1±1.7 cm for DCIS, 2.7±1.7 cm for DCIS-Mi, and 2.5±1.5 cm for DCIS-IDC. The tumor size of DCIS was significantly smaller than that of DCIS-Mi (P=0.002) and DCIS-IDC (P=0.000), but no significant difference was found between DCIS-Mi and DCIS-IDC (P=0.665) by the Mann-Whitney U test. The proportions of comedonecrosis were 10.8% in DCIS, 30.7% in DCIS-Mi, and 3.7% in DCIS-IDC, and significant differences were found between the groups under the Bonferroni adjusted *P* value. The proportions of multifocal lesions in the three groups were 20.1% in DCIS, 25% in DCIS-Mi, and 13% in DCIS-IDC, and the value in DCIS-IDC was significantly lower than that in the other two groups, but no difference was found between DCIS and DCIS-Mi under the Bonferroni adjusted *P* value. The rates of lymph node metastasis were 0.5% in DCIS, 13.3% in

**Table 1.** Pathologic features of the three groups: DCIS, DCIS-Mi, and DCIS-IDC

| | DCIS | | DCIS-Mi | | DCIS-IDC | | *P*-value |
|---|---|---|---|---|---|---|---|
| | (n=453) | % | (n=88) | % | (n=269) | % | |
| Sex | | | | | | | |
| female | 444 | 99.6 | 87 | 100 | 269 | 0 | 0.626* |
| male | 2 | 0.4 | 0 | 0 | 0 | 0 | |
| Age | | | | | | | |
| ≤30 | 10 | 2.2 | 0 | 0 | 7 | 2.6 | 0.374# |
| 30-40 | 73 | 16.1 | 20 | 23.0 | 37 | 13.8 | |
| 40-50 | 179 | 39.5 | 30 | 34.5 | 107 | 39.9 | |
| 50-60 | 128 | 28.3 | 25 | 28.7 | 68 | 25.4 | |
| 60-70 | 47 | 10.4 | 10 | 11.5 | 40 | 14.9 | |
| >70 | 16 | 3.5 | 2 | 2.3 | 9 | 3.4 | |
| Side | | | | | | | |
| left | 245 | 54.1 | 48 | 54.5 | 145 | 53.9 | 0.994* |
| right | 208 | 45.9 | 40 | 45.5 | 124 | 46.1 | |
| Nuclear grade | | | | | | | |
| low | 109 | 24.6 | 4 | 4.7 | 21 | 8.7 | 0.000# |
| moderate | 156 | 35.2 | 15 | 17.6 | 72 | 29.8 | |
| high | 178 | 40.2 | 66 | 77.6 | 149 | 61.6 | |
| unknown | 10 | | 3 | | 27 | | |
| Tumor size (cm) | | | | | | | |
| ≤2 | 246 | 61.8 | 29 | 42.0 | 93 | 46.0 | 0.000# |
| 2-5 | 130 | 32.7 | 35 | 50.7 | 99 | 49.0 | |
| >5 | 22 | 5.5 | 5 | 7.2 | 11 | 5.4 | |
| unknown | 55 | | 19 | | 67 | | |
| Multifocal lesion | | | | | | | |
| no | 362 | 79.9 | 66 | 75.0 | 234 | 87.0 | 0.013* |
| yes | 91 | 20.1 | 22 | 25.0 | 35 | 13.0 | |
| Acne-like necrosis | | | | | | | |
| absent | 404 | 89.2 | 61 | 69.3 | 259 | 96.3 | 0.000* |
| present | 49 | 10.8 | 27 | 30.7 | 10 | 3.7 | |
| Lymph node metastasis | | | | | | | |
| negative | 392 | 99.5 | 72 | 86.7 | 129 | 59.7 | 0.000* |
| positive | 2 | 0.5 | 11 | 13.3 | 87 | 40.3 | |
| unknown | 59 | | 5 | | 53 | | |
| ER | | | | | | | |
| negative | 124 | 30.1 | 50 | 59.5 | 54 | 21.0 | 0.000* |
| positive | 287 | 69.9 | 34 | 40.5 | 203 | 79.0 | |
| unknown | 42 | | 4 | | 12 | | |
| PR | | | | | | | |
| negative | 141 | 34.3 | 47 | 56.0 | 64 | 24.9 | 0.000* |
| positive | 270 | 65.7 | 37 | 44.0 | 193 | 75.1 | |
| unknown | 42 | | 4 | | 12 | | |
| HER2 | | | | | | | |
| negative | 198 | 48.2 | 28 | 33.3 | 131 | 51.0 | 0.003# |
| indeterminate | 79 | 19.2 | 16 | 19.0 | 56 | 21.8 | |
| positive | 134 | 32.6 | 40 | 47.6 | 70 | 27.2 | |
| unknown | 42 | | 4 | | 12 | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ki67 | | | | | | | |
| low expression | 201 | 59.5 | 14 | 25.0 | 71 | 28.3 | 0.000* |
| high expression | 137 | 40.5 | 42 | 75.0 | 180 | 71.7 | |
| unknown | 115 | | 32 | | 18 | | |
| Subtype | | | | | | | |
| luminal A | 115 | 39.8 | 0 | 0 | 50 | 25.1 | 0.000* |
| luminal B | 82 | 28.4 | 17 | 30.4 | 106 | 53.3 | |
| HER2+ subtype | 54 | 18.7 | 11 | 19.6 | 33 | 16.6 | |
| HER2- subtype | 28 | 9.7 | 6 | 10.7 | 73 | 36.7 | |
| HER2 overexpression | 80 | 27.7 | 29 | 51.8 | 37 | 18.6 | |
| basal-like | 12 | 4.2 | 10 | 17.9 | 6 | 3.0 | |
| unknown | 164 | | 32 | | 70 | | |

*performed with the Pearson's chi-square test; #performed with the Kruskal-Wallis test.

DCIS-Mi, and 40.3% in DCIS-IDC, with significant differences between any two groups under the Bonferroni adjusted *P* value by the chi-square test.

*Immunohistochemical findings*

There was a significant difference in the expression of ER and PR between the three groups by the Bonferroni adjusted *P* value (P=0.000 for ER and PR), and the positive rate was highest in DCIS-IDC, next highest in DCIS, and lowest in DCIS-Mi (ER: DCIS-IDC 79.0% vs. DCIS 69.9% vs. DCIS-Mi 40.5%; PR: DCIS-IDC 75.1% vs. DCIS 65.7% vs. DCIS-Mi 44.0%). There was also a significant difference in the expression of HER2 in the three groups by the Kruskal-Wallis test (the positive rate was DCIS 32.6% vs. DCIS-Mi 47.6% vs. DCIS-IDC 27.2%, P= 0.003). DCIS-Mi had a significantly higher expression rate than DCIS (P=0.001) and DCIS-IDC (P=0.001), but the expression in DCIS and DCIS-IDC was similar by the Mann-Whitney U test (P=0.269). There was also a significant difference in the expression of Ki67 in the three groups by the chi-square test (the proportion of high-expressed Ki67 was DCIS 40.5% vs. DCIS-Mi 75% vs. DCIS-IDC 71.7%, P=0.000). The expression rate in DCIS-Mi and DCIS-IDC was significantly higher than that in DCIS, while DCIS-Mi and DCIS-IDC showed no difference under the Bonferroni adjusted *P* value.

*Subtype based on IHC surrogate classification*

The composition of subtypes was different between the three groups (P<0.001). Further intergroup comparisons were performed with a Bonferroni adjusted *P* value. There was no difference in the proportion of the luminal B HER2+ subtype, HER2 overexpression subtype and basal-like subtype between DCIS and DCIS-IDC, but a significant difference was found in the proportion of the luminal A subtype and luminal B HER2- subtype between them. Luminal A was the dominant subtype (39.8%) in DCIS, while luminal B (HER2-) was the dominant subtype (36.7%) in DCIS-IDC. Significant differences were found in the proportion of each subtype except for the luminal B subtype between DCIS and DCIS-Mi. A similar situation occurred when comparing DCIS-Mi and DCIS-IDC, and significant differences were found in the proportion of each subtype except for the luminal B HER2+ subtype. Overall, the dominant subtypes of DCIS and DCIS-IDC were luminal types (with luminal A accounting for 39.8% in DCIS and luminal B accounting for 53.3% in DCIS-IDC), while the dominant subtype of DCIS-Mi was HER2 overexpression (accounting for 51.8%).

*Agreement between infiltrative and noninfiltrative components of DCIS-IDC/Mi*

There were 39 cases of DCIS-IDC/Mi with accompanying IHC results of the DCIS component and IDC/Mi component simultaneously in the archival reports. Among these, 37 cases were the same in the IHC surrogate classification, and 34 patients had the same ER/PR/HER2 status. There was no significant difference in the expression of ER, PR, HER2, and Ki67 between the two components (ER, P= 1.000; PR, P=1.000; HER2, P=0.320; Ki67, P=0.289). In conclusion, the IHC expression between infiltrative and noninfiltrative components of DCIS-IDC/Mi showed good consistency (**Table 2**).

**Table 2.** Agreement between infiltrative and noninfiltrative components of DCIS-IDC/Mi

| ER | | IDC/Mi component | | McNemar *P* value |
|---|---|---|---|---|
| | | Negative | Positive | |
| DCIS component | Negative | 25 | 1 | 1.000 |
| | Positive | 1 | 12 | |
| PR | | IDC/Mi component | | McNemar *P* value |
| | | Negative | Positive | |
| DCIS component | Negative | 21 | 2 | 1.000 |
| | Positive | 2 | 14 | |
| Ki67 | | IDC/Mi component | | McNemar *P* value |
| | | Low expression | High expression | |
| DCIS component | Low expression | 21 | 6 | 0.289 |
| | High expression | 2 | 10 | |
| HER2 | | DCIS component | IDC/Mi component | Pearson *P* value |
| HER2 | Negative | 8 | 14 | 0.320 |
| | Indeterminate | 11 | 9 | |
| | Positive | 20 | 16 | |

*IHC differences between DCIS-Mi and DCIS-IDC T1a-b*

In DCIS-IDC, T1a-b tumors had smaller invasive lesions that were similar to those in DCIS-Mi (there were too few T1a cases in this study to carry out statistical analysis). Compared with T1a-b tumors, DCIS-Mi still had a lower expression rate of ER and PR (P=0.001 and P=0.006, respectively) and a higher expression rate of HER2 (P=0.015), which was consistent with the comparison between DCIS-Mi and DCIS-IDC. However, a significantly higher expression of Ki67 was found in DCIS-Mi than in T1a-b tumors (P=0.003) (**Table 3**).

## Discussion

Compared with pure DCIS, DCIS-IDC was significantly more often associated with high nuclear grade, large tumor size, high Ki67 index, and lymph node metastasis. Due to the high expression of Ki67 in DCIS-IDC, the luminal B HER2- subtype (36.7%) replaced luminal A (39.8%) as the dominant type according to IHC surrogate classification. Of note, the differences in expression of ER, PR, and HER2 between pure DCIS and DCIS-IDC are still controversial. Schorr et al found a lower steroid receptor expression rate in DCIS-IDC than in DCIS [10], while Steinman et al observed no significant difference between them in the expression of ER, PR, and HER2 [11]. In our study, higher expression of steroid receptors was shown in DCIS-IDC than in DCIS, but the status of HER2 between the two groups was similar. The discrepancy in steroid receptor expression between different studies may be partly due to the different interpretation standards for steroid receptors used. In addition, Jang et al found that the rate of HER2 amplification was similar between DCIS and DCIS-IDC, but when stratified by the histologic grade of carcinoma, amplification was more frequently seen in high-grade DCIS than in high-grade DCIS-IDC [15].

Although DCIS-Mi is defined as a very early stage of invasive cancer with an invasive lesion less than 1 mm, it also shows more aggressive characteristics than DCIS. In our study, DCIS-Mi was significantly associated with high nuclear grade, large tumor size, and comedonecrosis. In terms of IHC molecular characteristics, the rate of absence of ER/PR expression, the rate of positive HER2 expression, and the expression of Ki67 were significantly higher than those in the DCIS group. According to the IHC surrogate classification, more than half (51.8%) of DCIS-Mi cases were HER2-overexpression subtype, while nearly half (49.5%) of DCIS cases were the HER2-negative luminal subtype. These findings were consistent with previous studies [6, 16, 17]. Ozkan-Gurdal et al found that comedonecrosis and hormone receptor (ER and/or PR) negativity were independent predictors for microinvasion when the influence of tumor size and high nuclear grade were excluded [18]. Kim et al found that large tumor

**Table 3.** IHC differences between DCIS-Mi and DCIS-IDC T1a-b

| | DCIS-Mi | | DCIS-IDC T1a-b | | *P* value |
|---|---|---|---|---|---|
| ER | | | | | |
| negative | 50 | 59.5% | 3 | 15.8% | 0.001* |
| positive | 34 | 40.5% | 16 | 84.2% | |
| PR | | | | | |
| negative | 47 | 56.0% | 4 | 21.1% | 0.006* |
| positive | 37 | 44.0% | 15 | 78.9% | |
| HER2 | | | | | |
| negative | 28 | 33.3% | 12 | 63.2% | 0.015# |
| indeterminate | 16 | 19.0% | 3 | 15.8% | |
| positive | 40 | 47.6% | 4 | 21.1% | |
| Ki67 | | | | | |
| low expression | 14 | 25.0% | 12 | 63.2% | 0.003* |
| high expression | 42 | 75.0% | 7 | 36.8% | |

*performed with the Pearson's chi-square test; #performed with the Kruskal-Wallis test.

size, comedonecrosis, and ER negative status were independent risk factors, but high nuclear grade, PR negativity, HER2 positivity, and overexpression/high expression of p53 and Ki67 were not [19].

Interestingly, even compared with DCIS-IDC, DCIS-Mi still maintains these distinct pathologic features. The proportions of cases with high nuclear grade, comedo necrosis, and multifocal lesions in DCIS-Mi were still significantly higher than those in DCIS-IDC, while the tumor size of the two groups was similar. The expression rate of steroid receptors in DCIS-Mi was the lowest in the three groups, while the rate of positive HER2 expression was the highest in the DCIS-Mi group. Although the Ki67 index in DCIS-Mi was not significantly different from that in DCIS-IDC, it was higher than that in T1a-b stage DCIS-IDC. These findings concur with those of a cohort study comparing DCIS, DCIS-Mi, and T1a IDC in 134,569 cases from the SEER database [20]. Similar findings were also found in the report by Yu et al [7] comparing DCIS, DCIS-Mi, and DCIS-IDC and the report by Zhang et al [21] comparing DCIS, DCIS-Mi, and IDC.

We acknowledge that there are several limitations in this study. First, as it is a retrospective analysis, there were variations in archival pathologic report styles and loss of pathologic data in some cases. Second, the IHC data of DCIS-IDC involved in the analysis were represented by that of the IDC component. Although previous studies found no significant difference in ER, PR, and HER2 expression between the two components of the same tumor [10, 11], and the analysis of 39 cases of DCIS-IDC/Mi in our study further proves the agreement between them, comprehensive IHC data containing both intraductal and invasive components will be more convincing. Third, HER2 was tested by IHC only, and indeterminate HER2 status was not further confirmed by fluorescence in situ hybridization.

In conclusion, our study found significant pathologic differences between DCIS, DCIS-Mi, and DCIS-IDC. Impressively, DCIS-Mi represents a distinct entity, which suggests that when DCIS is found to possess features including high nuclear grade, large tumor size, comedonecrosis, steroid receptor negativity, HER2 positivity, and high Ki67 expression, more careful screening should be performed to check for coexisting microinvasion. Compared with DCIS, DCIS-IDC had higher nuclear grade, larger tumor size, higher expression of steroid receptors, and higher Ki67 index, but had equivalent HER2 status. More studies with unified interpretation standards and subgroup analyses, if needed, are required to verify the status of steroid receptors between them.

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## Disclosure of conflict of interest

None.

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