Comparison of breast ductal carcinoma in situ and ductal carcinoma in situ with microinvasion, and analysis of axillary lymph node metastasis

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Abstract

To compare the clinicopathologic features and long-term outcomes for women with ductal carcinoma in situ (DCIS) vs DCIS with microinvasion (DCISM), to assess the impact of microinvasion on tumor size and determine relationships between the number of microinvasive lesions and clinicopathological factors.

A total of 493 patients with DCIS or DCISM from our database were analyzed to assess differences in clinicopathologic features and outcomes between the 2 cohorts.

The median follow-up was 3.9 years, 229 patients had DCIS and 264 had DCISM, and the mean age was 46.8 years for the entire group. A total of 208 patients underwent axillary operation in the DCIS cohort vs 246 in the DCISM cohort, and the number of lymph node metastasis cases was 0 vs 13 for the 2 groups. For the lymph node-positive cases, the proportion of patients with no less than 3 microinvasive legions was 61.5% (8/13), while in the lymph node-negative group, the proportion of patients was 31.1% (78/251) ($P < .05$). For the DCIS and DCISM groups, the relapse-free survival (RFS) values were 99.0% and 95.4% ($P = .034$), while the overall survival (OS) values were 96.2% and 99.2% ($P = .032$), respectively.

Our data imply that for breast DCIS patients, axillary lymph node operation can be avoided, but for DCISM patients, surgical evaluation of the axilla is necessary. In addition, having no less than 3 microinvasive lesions in DCISM indicates poor prognosis. In the pathological staging of DCISM, tumor size and number of microinvasive lesions should be considered.

Abbreviations: AJCC = the American Joint Committee on Cancer, ALND = axillary lymph node dissection, DCIS = ductal carcinoma in situ, DCISM = ductal carcinoma in situ with microinvasion, ER = estrogen receptor, Her2 = Human epidermal growth factor receptor 2, OS = overall survival, PR = progesterone receptor, RFS = relapse-free survival, RT = radiotherapy, SLNB = sentinel lymph node biopsy.

Keywords: microinvasive breast cancer, ductal carcinoma in situ, ductal carcinoma in situ with microinvasion, early-stage breast cancer

1. Introduction

Breast cancer is one of the most common malignant tumors in women [1]. In recent years, the incidence of breast cancer has shown an increasing trend in China [2]. With medical advances, especially due to the extensive use of mammographic imaging, the number of patients with ductal cancer in situ (DCIS) and DCIS with microinvasion (DCISM) is increasing [3]. DCIS is defined as a neoplastic proliferation of epithelial cells confined to the ductal-lobular system without tumor invasion through the basement membrane [4]. According to the criteria of the American Joint Committee on Cancer (AJCC), DCISM is defined as DCIS with a microscopic focus of invasion ≤1 mm in longest diameter [5]. Breast DCIS and DCISM are considered to have satisfactory prognoses. Surgical evaluation of the axilla, with either sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND), is typically not performed for pure DCIS lesions because of the low prevalence of nodal metastasis (0%–14%).[6–11] Some studies have revealed that DCISM has potential for invasion and metastasis.[12,13] The present study assessed the utility of commonly available clinical pathologic parameters such age, family history, receptor status, etc., for determining prognosis in DCIS and DCISM. The axillary lymph node metastasis of DCIS and DCISM was also analyzed. At present, the clinical stage of invasive breast cancer is based on the size of the invasive focus,[5] but the stage of DCISM is pTmi (focus of invasion ≤1 mm) regardless of tumor size. Whether the tumor size will affect the probability of axillary lymph node metastasis or be related to prognosis and whether the number of microinvasive lesions in DCISM will affect the probability of axillary lymph node metastasis or be related to prognosis are the focus of this study.

2. Patients and methods

2.1. Patients

This study retrospectively collected 493 patients with a pathologic diagnosis of breast DCIS or DCISM from the Departments of Hebei Breast Center, the Fourth Hospital of Hebei Medical University, between 2011 and 2018. In this study, DCISM was defined as a subtype of DCIS with limited microscopic (≤1.0 mm) stromal invasion beyond the basement membrane. The lump size was defined as the size of the tumor in the clinical examination, and the tumor size was defined as the size of the tumor after the operation. Surgical evaluation of the axilla with either full ALND or SLNB was performed at the discretion of the treating surgeon. Adjuvant radiotherapy (RT), systemic chemotherapy and/or adjuvant hormone therapy were administered as indicated in accordance with standard practices at the time of this study. The study was approved by the ethics committee of the Fourth Hospital of Hebei Medical University.

2.2. Statistical analysis

All patient data, including pathology status (DCIS vs DCISM) and relevant covariables, were entered into a computerized database and analyzed. All tests of statistical significance were 2 sided. Probability (P) values of <.05 were considered statistically significant. The study endpoints were relapse-free survival (RFS) and overall survival (OS), including all deaths. Disease relapse included locoregional recurrence, contralateral breast cancer, and distant metastases. Locoregional recurrence was defined as clinically and biopsy-proven relapse in the ipsilateral breast or chest and/or recurrence in the regional lymph nodes, and distant metastasis was defined as distant disease according to clinical and/or radiographic evidence. The endpoints were calculated from the date of surgery or RT completion. Median follow-up was calculated by the reverse Kaplan–Meier method. Tests of association and correlation were conducted by using the $n \times n$ Pearson χ^2 test (or Fisher exact test when appropriate). Statistical analyses were performed using SPSS software version 13.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Descriptive statistics

In this stud, 493 patients were included, 229 of whom had pure DCIS and 264 of whom had DCISM. The mean age at diagnosis of the entire cohort was 46.8 years, and the median follow-up was 3.9 years. In the DCIS cohort, the vast majority of patients went underwent consultation because of a lump, nipple discharge or papillary erosion, and only 21 patients were treated for microcalcification. In the DCISM cohort, the majority of patients were treated for a lump or nipple discharge, and only 11 patients were treated for microcalcification. Table 1 summarizes the frequency statistics for the clinicopathologic characteristics of the patient cohort, including age, family history, clinical examination, mammography with microcalcification, lump size, and molecular marker data. There was no difference between the DCIS and DCISM cohorts with respect to age at presentation, or family history (1 or more first-degree relatives with a diagnosis of breast cancer). The estrogen receptor (ER), progesterone receptor (PR) and Her2 (Human epidermal growth factor receptor 2) statuses were different for each cohort: the proportion of patients

Table 1

Association between prognostic factor(s) and pathology.

Prognostic factor	Pathology		P
	DCIS	DCISM	
Age(y)			.54
<50	120	131	
≥50	109	133	
Family history			.3
Positive	38	54	
Negative	191	210	
Clinical symptom			<.01
Lump	194	241	
Nipple discharge	28	52	
Papillary erosion (without tumor)	6	0	
Negative	21	11	
Mammography with microcalcification			.06
Positive	72	128	
Negative	99	120	
Lump size			<.01
≤2 cm	101	119	
>2 cm	35	106	
Tumor resection	58	16	
Estrogen receptor			<.01
Positive	168	143	
Negative	61	121	
Progesterone receptor			<.01
Positive	161	122	
Negative	68	142	
Her2			<.01
Positive	45	108	
Negative	184	156	

who were ER positive was 73.4% in the DCIS group and 54.2% in the DCISM group (P < .01); the proportion of patients who were PR positive was 73.4% in the DCIS group and 46.2% in the DCISM group (P < .01); the proportion of patients who were Her2 positive was 19.7% in the DCIS group and 40.9% in the DCISM group, P < .01.

Table 2 summarizes the treatment of the 2 patient cohorts. In the DCIS cohort, 19 patients underwent breast-conserving operations, 209 patients underwent mastectomy, and 1 patient underwent Mammotome-based atherectomy (refused further

Table 2

Treatment of 2 patient cohorts.

Prognostic factor	DCIS	DCISM	P
Operation			1
Breast conserving	19	23	
Mastectomy	209	241	
Axillary lymph nodes			<.01
Positive	0	13	
Negative	208	233	
Endocrine therapy			.37
Yes	120	149	
No	109	115	
Chemotherapy			<.01
Yes	0	39	
No	229	225	
Radiotherapy			.25
Yes	10	19	
No	219	245	

Table 3

Analysis of axillary lymph node positive patients.

	Lymph node		
	Positive	Negative	
Tumor size			0.39
≤2 cm	5	127	
>2 cm	8	108	
Estrogen receptor			0.58
Positive	8	132	
Negative	5	119	
Progesterone receptor			0.58
Positive	7	112	
Negative	6	139	
Her2			0.57
Positive	4	106	
Negative	9	145	
Number of microinvasion			0.03
≥3	8	78	
1–2	5	173	

therapy). In the DCISM cohort, 23 patients underwent breast-conserving operations, and 241 patients underwent mastectomy. In the DCIS cohort, 208 patients underwent axillary operation (151 underwent SLNB, and 57 underwent ALND), and no lymph node metastasis was observed. In the DCISM cohort, 246 patients underwent axillary operation (164 underwent SLNB, and 82 underwent ALND), and 13 patients had lymph node metastasis. Compared with the value in the DCIS group, the rate of positive axillary lymph nodes was 5.3% in the DCISM group ($P < .01$). None of the DCIS cohort received chemotherapy, and 39 patients in the DCISM cohort received chemotherapy ($P < .01$). There was no difference in the percentages of patients who accepted endocrine therapy or radiotherapy.

Table 3 summarizes the analysis of patients with axillary lymph node metastasis. In the 264 patients with DCISM, 246 patients received axillary operation, and 13 patients had lymph node metastasis. In this study, the number of microinvasive lesions was determined: 175 patients had a single microinvasive lesion, 3 patients had 2 microinvasive lesions, and 86 patients had no less than 3 microinvasive lesions. The number of lesions was correlated with tumor size. For the lymph node-positive patients, the proportion of patients with no less than 3 microinvasive lesions was 61.5% (8/13), compared with 31.1% (78/251) in those patients without lymph node metastasis ($P < .05$). There were no differences in tumor size or ER, PR, or HER2 status between the 2 groups.

In this study, 444 patients were followed up (207 patients with DCIS and 237 patients with DCISM), the survival rate was 90.1%, and the median follow-up was 3.9 years. Kaplan–Meier survival curves for RFS and OS with respect to pathology are presented in Figures 1 and 2. As shown in Figure 1, a total of 2 patients (0.96%) with DCIS (1 case patient with locoregional recurrence and, 1 patients with contralateral breast cancer) and 11 patients (4.64%) with DCISM (7 patients with locoregional recurrence, 2 patients case with contralateral breast cancer, and 2 patients with distant metastases) experienced disease relapse, for the RFS rates of 99.0% and 95.4%, respectively ($P = .034$, log-rank test). For relapsed patient, the proportion of patients with no less than 3 microinvasive lesions was 63.6% (7/11), compared with 31.2% (79/253) in patients who did not have relapse ($P < .05$). As seen in Figure 2, there were a total of 7 deaths
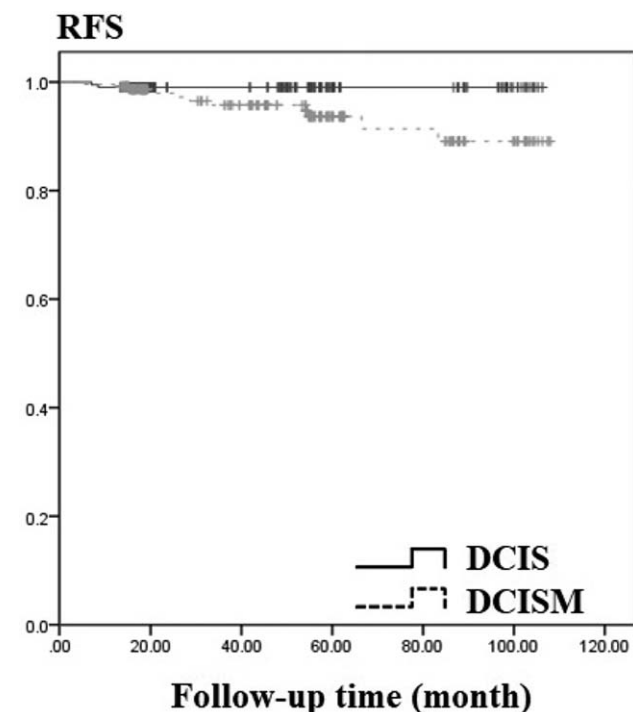

Figure 1. Relapse-free survival (RFS) in breast ductal carcinoma in situ (DCIS) and ductal carcinoma in situ with microinvasion (DCISM).

(3.38%) in the DCIS cohort (all deaths were unrelated to breast cancer) and 2 deaths (0.84%) in the DCISM cohort (1 death related to breast cancer metastasis and 1 death unrelated to breast cancer), for resulting in OS rates of 96.6% and 99.2%, respectively ($P = .032$, log-rank test).

3.2. Discussion

In our study of 493 women with breast DCIS or DCISM, the findings suggest that both diseases have a satisfactory prognosis. The proportions of patients with locoregional recurrence, contralateral breast cancer, or distant metastasis were 0.96% and 4.64% in the DCIS and DCISM groups, respectively. In the DCIS cohort, all deaths were unrelated to breast cancer, and in the DCISM cohort, there were only 2 deaths. The occurrence of lymph node or distant metastasis in DCIS is controversial. As reported, the prevalence of nodal metastases in pure DCIS lesions is 0% to 14% [6–11]. Instances of lymph node metastasis in DCIS may actually be the result of small microinvasive foci that are missed on pathologic examination of the breast specimen. This type of missed diagnosis is more common in larger DCIS lesions, in which the accuracy of histologic assessment in detecting small areas of invasion is limited. Epithelial-mesenchymal transitions has been proposed to explain the mechanism of metastasis in DCIS,[14] but results are still preliminary. If true, this theory will complicate clinical diagnosis and treatment, likely leading to overtreatment of DCIS. However, we propose that pure DCIS will not metastasize, and the smaller the tumor size is, the more accurate the diagnosis. In this study, among 229 DCIS patients, excluding elderly patients or those with underlying diseases, 208 patients underwent axillary operation, and there were no cases of lymph node metastasis. The follow-up results showed no
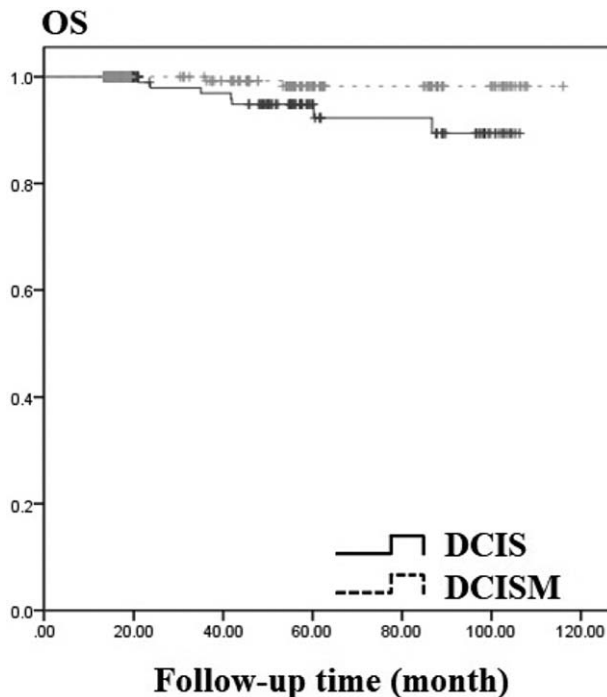
Figure 2. Overall survival (OS) in breast ductal carcinoma in situ (DCIS) and ductal carcinoma in situ with microinvasion (DCISM).

recurrence in axillary lymph nodes. Based on these findings, we believe that for breast DCIS patients, axillary lymph node operation can be avoided.

In this study, the proportion of patients who underwent breast-conserving operations was low: only 19 patients (8.3%) in the DCIS cohort and 23 patients (8.7%) in the DICISM cohort. However, both DCIS or DCISM include extensive micro-calcification, nipple discharge and papillary erosion (Paget disease), which are contraindications of breast-conserving operations. In addition, many patients who were suitable for breast-conserving surgery refuse it, and the proportion of patients undergoing breast-conserving surgery was low in our department. Therefore, in the clinical, we should fully communicate with patients and improve the proportion willing to undergo breast-conserving treatment. Axillary lymph node operation could be avoided in DCIS patients who receive breast-conserving treatment. Compared with the DCIS group, the DCISM group had a higher proportion of patients with lymph node metastasis. In the DCISM cohort, 13 (5.3%) patients had lymph node metastasis, and the DCISM group had significantly worse RFS than the DCIS group, with 11 patients (4.64%) experiencing relapse and 6 patients experiencing ipsilateral lymph node metastasis. Therefore, for DCISM, surgical evaluation of the axilla is necessary.

At present, the clinical stage of invasive breast cancer is based on the size of the invasive focus,[5] but the stage of DCISM is pTmi (focus of invasion ≤1 mm) regardless of tumor size. Regarding the number of microinvasive lesions in this study, 175 patients had a single microinvasive lesion, 3 patients had 2 microinvasive lesions, and 86 patients had no less than 3 microinvasive lesions. In this study, we found that no less than 3 microinvasive lesions in DCISM indicated a worse prognosis than 1 or 2 microinvasive lesions. Patients with no less than 3 microinvasive lesions were more likely

to have axillary lymph node metastasis than those with 1 or 2 microinvasive lesions. For patients with lymph node metastasis, the proportion of patients with no less than 3 microinvasion lesions was 61.5%, compared with lymph node negative 31.1% in patients without lymph node metastasis. In addition, patients with no less than 3 microinvasive lesions were more likely to relapse. For patients who experienced relapse, the proportion of patients with no less than 3 microinvasion lesions was 63.6%, compared with 31.2% in patients who did not relapse. Having more microinvasive lesions was more common in patients with larger DCISM lesions than in those with smaller lesions. The number of lesions was correlated with tumor size. However, in this study, the proportion of patients with tumor size >2 cm was 61.5% (8/13) in the group of patients with lymph node metastasis and 54.5% (6/11) in patients who relapsed, and the results were not significantly different. This may be related to the low number of patients with lymph node metastasis and the short follow-up time for DCISM patients. We suggest that, tumor size and the number of microinvasive lesions are prognostic factors for DCISM and therefore should be considered in the pathological staging of breast cancer.

It is difficult to choose appropriate treatment for patients with DCISM.[15] In this study, 13 patients had lymph node metastasis (5.3%) and 6 patients had ipsilateral lymph node metastasis in the DCISM cohort; there were 39 patients (14.8%) with DCISM who received chemotherapy. Do determine whether chemotherapy can improve the prognosis of DCISM patients, especially patients with DCISM without lymph node metastasis, long-term follow-up data are needed.

Mammography is sensitive to calcification and can improve the detection rate of DCIS or DCISM, reducing mortality [16]. A remarkable increase in the incidence of DCIS and DCISM has been observed in the most recent decade, as the use of screening mammography has become widespread.[17,18] In this study, the proportion of patients with microcalcification on mammography in the DCIS and DCISM cohorts was 31.4% and 48.5%, respectively. However, in the DCIS cohort, only 21 patients (9.2%) were treated for the microcalcification, and in the DCISM cohort, only 11 patients (4.2%) were treated for the micro-calcification. The vast majority of patients underwent consultation because of a lump, nipple discharge or papillary erosion. These results reflect the need for people pay attention to self-health and improve their knowledge of breast cancer.

In conclusion, for breast DCIS patients, axillary lymph node operation can be avoided, but for DCISM patients, surgical evaluation of the axilla is necessary. In addition, having no less than 3 microinvasive lesions in DCISM indicates poor prognosis. In DCISM, tumor size and the number of microinvasive lesions should be considered in the pathological staging.

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