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Original Article

Long term prognosis of ductal carcinoma *in situ* with microinvasion: a retrospective cohort study

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Abstract: Ductal carcinoma *in situ* with microinvasion (DCIS-Mi) is an early-stage breast cancer with long-term behavior, prognosis and treatment not fully understood. The aim of our study was to explore the clinicopathological and prognostic features of DCIS-Mi with pure DCIS and IDC-T1 (invasive ductal carcinoma with a tumor size ≤2 cm) as control. We retrospectively reviewed 242 cases of DCIS-Mi, 280 cases of pure DCIS, and 347 cases of IDC-T1. The clinicopathological features, therapeutic schemes and survival status were compared among the three groups. After a median follow-up of 109 months, the 5-year disease-free survival (DFS) was lower for the DCIS-Mi patients than for the DCIS patients but higher than the IDC-T1 patients (100%, 96.89% and 87.86% respectively, $P<0.001$). The 5-year breast cancer specific survival for DCIS-Mi patients was also between that of DCIS and IDC-T1 patients (100%, 99.32%, and 95.42% respectively, $P=0.001$). Tumor size ($P<0.001$, HR=18.31, 95% confidence interval (CI) 5.53-60.65) was identified as an independent prognostic factor for recurrence or metastasis. Furthermore, our study indicated that DCIS-Mi patients derived minimal, if any, benefit from chemotherapy treatment after mastectomy ($P=0.63$, HR=1.50, 95% CI 0.29-7.87). To our knowledge, this is the largest follow-up cohort study on Chinese DCIS-Mi patients. Our data suggested that DCIS-Mi exhibited worse clinical outcome than pure DCIS but better than that of IDC-T1. Tumor size was an independent prognostic factor. Post-mastectomy chemotherapy did not help for increasing DFS for DCIS-Mi patients.

Keywords: Breast neoplasms, carcinoma, intraductal, non-infiltrating, microinvasion, clinicopathological characteristics, prognosis

Introduction

Ductal carcinoma *in situ* with microinvasion (DCIS-Mi) is defined as ductal carcinoma *in situ* (DCIS) with no invasive foci larger than 1 mm by the American Joint Committee on Cancer (AJCC 7th edition) [1]. This group of breast cancer is estimated taking up 10-20% of DCIS cases and accounts for approximately 1% of all breast cancers [2, 3]. As mammography and advanced technologies were widely used, early-stage breast cancer, e.g. DCIS with/without microinvasive carcinomas were diagnosed for the last 3 decades by over five folds. Currently DCIS with/without microinvasive carcinoma accounts for approximately 20% to 25% of newly diagnosed breast cancer in the United States [4], while accounts for approximately 10 to 15 % in China [5].

Although several groups have reported the histopathologic features and clinical outcomes for DCIS-Mi, there remain plenty of controversial tissues on the biological behavior, natural history, prognosis, as well as optimal treatment regimen [6-10]. The clinicopathologic characteristics, long-term behavior, prognostic implications and treatment modalities of DCIS or DCIS-Mi are poorly understood in Chinese patients due to lack of studies for large-scale and long term follow-up cohort [8]. In order to precisely estimate the prognosis of this group of patients, we conduct a large cohort study with a long-term follow-up.

Chemotherapy has been increasingly used to reduce tumor local recurrence or distant metastasis by exterminating residual tumor cells after surgery. The National Comprehensive

Cancer Network Guidelines® for breast cancer (V2.2017) suggests that patients with DCIS-Mi should be considered for adjuvant chemotherapy according to axillary node status. However, although most patients with DCIS-Mi receive postoperative chemotherapy in China, there is insufficient evidence indicating that those patients obtain any benefit from adjuvant chemotherapy. Therefore, part of DCIS-Mi patients may receive overtreatment of chemotherapy.

In this study, we assessed the clinicopathologic characteristics and long-term outcomes of DCIS-Mi patients with different clinical treatment regimens, and tried to identify prognostic factors as well as optimized regimens for certain subgroups of patients.

Materials and methods

Patient selection

Patients, who were diagnosed with breast cancer from 1997 to 2014 in the West China Hospital and the Fourth Hospital of Hebei Medical University, were retrospectively reviewed. Women with histologically confirmed pure DCIS, DCIS-Mi, and IDC-T1 were eligible for recruitment. Treatment with surgery to negative margins (confirmed by pathologists) was required. A total of 869 patients who had complete clinical and pathological data were selected. All diagnoses were confirmed by two pathologists in the Department of Pathology at West China Hospital. Pure DCIS was classified as a neoplastic proliferation of epithelial cells confined to the mammary ductal-lobular system in accordance with the World Health Organization Classification of Tumors. DCIS-Mi was defined as DCIS with no invasive focus measuring >1 mm in accordance with the 7th Edition of the AJCC Cancer Staging Manual [1]. Each invasive focus was measured individually, and the sizes of the foci in tumors with multiple foci of microinvasion were not added together. IDC-T1 was defined as IDC with a tumor size ≤2 cm and no distant metastasis (T1M0). The final study sample included 280 cases of pure DCIS, 242 cases of DCIS-Mi, and 347 cases of IDC-T1. All patients provided written informed consent.

Clinical and pathological variables

The estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/neu), and Ki-67 protein expression levels in both the *in situ* and invasive components were detected by immunohistochemistry (IHC). ER and PR expression were reported as positive if ≥1% of nuclei were stained and negative if <1% of tumor cells were stained. HER-2 expression was reported as positive if the IHC score was 3+ or positive fluorescence was detected using *in situ* hybridization (FISH). Cases with IHC scores of 0, 1+ or 2+ or without positive FISH were reported as negative. The Ki-67 index was computed as the proportion of cells with positive nuclear staining among at least 100 tumor cells examined in the surrounding area. Microinvasion was not always present on the deeper tissue sections used for the IHC studies. In these cases, the receptor profile for the *in situ* component alone was reported.

Surgery was coded as breast-conserving or mastectomy. Adjuvant therapy (chemotherapy, radiotherapy, endocrine therapy and targeted therapy) was coded as ever or never.

Follow-up and statistical analysis

Follow-up information and the survival status were obtained from the outpatient medical records of the patients and/or phone calls. The primary end point was disease-free survival (DFS), defined as the time from the date of diagnosis to the first documented recurrence of breast cancer. Breast cancer recurrence was categorized as locoregional disease (tumor in the breast or ipsilateral supraclavicular, subclavicular, internal mammary, or axillary nodes) or distant metastases. A secondary end point was breast cancer specific survival, defined as the time from the date of diagnosis to death of breast cancer.

Pearson's Chi-squared test (or Fisher's exact test when necessary) was used to compare the distribution of the clinical and pathological features between subgroups. DFS and breast cancer specific survival were estimated using Kaplan-Meier analysis, and the survival curves were compared using the log-rank test. Univariate and multivariate Cox regression analyses with stepwise selection were used to estimate the hazard ratios (HRs), 95% confidence intervals (CIs), and effects of clinical and pathological variables.

Table 1. Baseline characteristics of all patients

Characteristics	DCIS N=280 (%)	DCIS-Mi N=242 (%)	IDC-T1 N=347 (%)	*p*-value
Age (yrs.)				0.95
Age <50	168 (60.0)	143 (59.1)	204 (58.8)	0.83 (DCIS vs. DCIS-Mi)
Age ≥50	112 (40.0)	99 (40.9)	143 (41.2)	0.942 (DCIS-Mi vs. IDC-T1)
Breast surgery				<0.001*
Breast-conserving	33 (11.8)	26 (10.7)	13 (3.7)	0.71 (DCIS vs. DCIS-Mi)
Mastectomy	247 (88.2)	216 (89.3)	334 (96.3)	0.001* (DCIS-Mi vs. IDC-T1)
Tumor size (cm)				
T≤2	146 (52.1)	107 (44.2)	347 (100)	0.02* (DCIS vs. DCIS-Mi)
2<T≤5	122 (43.6)	111 (45.9)	-	
T>5	12 (4.3)	24 (9.9)	-	
Nuclear grade				<0.001*
Low	21 (7.5)	15 (6.2)	25 (7.2)	<0.001* (DCIS vs. DCIS-Mi)
Mid	126 (45.0)	64 (26.4)	137 (39.5)	0.002* (DCIS-Mi vs. IDC-T1)
High	133 (47.5)	163 (67.4)	185 (53.3)	
Necrosis				
Yes	143 (51.1)	132 (54.5)	-	0.43 (DCIS vs. DCIS-Mi)
No	137 (48.9)	110 (45.5)	-	
Lymph node status				<0.001* (DCIS-Mi vs. IDC-T1)
Negative	280 (100)	222 (91.7)	200 (57.6)	
Positive	-	20 (8.3)	147 (42.4)	
ER status				<0.001*
Negative	84 (30.0)	125 (51.7)	86 (24.8)	<0.001* (DCIS vs. DCIS-Mi)
Positive	196 (70.0)	117 (48.3)	261 (75.2)	<0.001* (DCIS-Mi vs. IDC-T1)
PR status				<0.001*
Negative	108 (38.6)	130 (53.7)	108 (31.1)	0.001* (DCIS vs. DCIS-Mi)
Positive	172 (61.4)	112 (46.3)	239 (68.9)	<0.001* (DCIS-Mi vs. IDC-T1)
HER2 status				<0.001*
0, 1+	137 (48.9)	84 (34.7)	265 (76.4)	0.001* (DCIS vs. DCIS-Mi)
2+	60 (21.4)	49 (20.2)	39 (11.2)	<0.001* (DCIS-Mi vs. IDC-T1)
3+	83 (29.6)	109 (45.0)	43 (12.4)	
Ki-67 index				0.001*
Ki-67 ≤14	109 (38.9)	108 (44.6)	104 (30.0)	0.19 (DCIS vs. DCIS-Mi)
Ki-67 >14	172 (61.1)	134 (55.4)	243 (70.0)	<0.001* (DCIS-Mi vs. IDC-T1)

DCIS, pure ductal carcinoma in situ; DCIS-Mi, ductal carcinoma *in situ* with microinvasion; IDC-T1, invasive breast cancer (T1M0); ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2. *Statistically significant.

To estimate the impact of chemotherapy on DFS for DCIS-Mi patients, we included patients treated with mastectomy alone or with mastectomy and adjuvant chemotherapy. Propensity score matching (PSM) was used to ensure that the clinicopathological features of the two subgroups of patients matched (i.e., tumor size). Then, we performed a Kaplan-Meier analysis to examine the DFS of these two subgroups.

All statistical tests were two-sided, and *p* values <0.05 were considered significant. The SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Clinical and pathological characteristics

Of 869 patients in this study, 280 were diagnosed as pure DCIS, 242 as DCIS-Mi, and 347 as IDC-T1. The baseline clinical and pathological features and the treatments between subgroups are shown in **Table 1**. The mean age

Table 2. Comparison of DCIS-Mi patients by treatments received

Therapeutic schemes	DCIS-Mi N=242 (%)
Breast-conserving	7 (2.9)
Breast-conserving + Radiotherapy	1 (0.4)
Breast-conserving + Chemotherapy	13 (5.4)
Breast-conserving + Radiotherapy + Chemotherapy	5 (2.1)
Mastectomy	68 (28.1)
Mastectomy + Radiotherapy	1 (0.4)
Mastectomy + Chemotherapy	131 (54.1)
Mastectomy + Radiotherapy + Chemotherapy	16 (6.6)

DCIS-Mi, ductal carcinoma *in situ* with microinvasion.

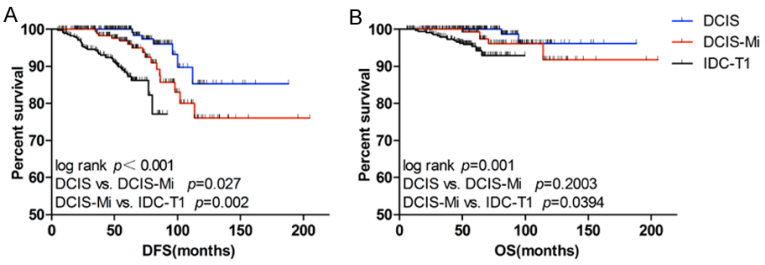

Figure 1. Long term prognosis of DCIS-Mi. A. DFS of different subgroups (log-rank *P*<0.0001). B. Breast cancer specific survival of different subgroups (log-rank *P*=0.001).

at the initial diagnosis was 49 (range 18-84) years old (yr.) for DCIS, 49.3 (range 26-89) yr. for DCIS-Mi, and 48.91 (range 29-80) yr. for IDC-T1.

In our study, patients with DCIS-Mi tumors were more likely to receive a breast-conserving surgery than patients with IDC-T1 (89.3% for DCIS-Mi, 96.3% for IDC-T1, *P*=0.001, **Table 1**).

Patients in the DCIS-Mi cohort had larger tumor sizes and more high-grade nuclei than patients in the DCIS cohort (9.9% vs. 4.3%, *P*=0.02 and 67.4% vs. 47.5%, *P*<0.001, **Table 1**). Patients with DCIS-Mi were more likely to have necrosis than patients with pure DCIS (54.5% for DCIS-Mi, 51.1% for DCIS), but the differences were not significant. There was a trend toward patients with IDC-T1 having more frequent axillary lymph node involvement (42.4% vs. 8.3%, P<0.001, **Table 1**) than patients with DCIS-Mi.

The proportions of ER and PR positivity in DCIS-Mi were 48.3% and 46.3%, respectively, which were slightly lower than the proportions in the pure DCIS and IDC-T1. Notably, the DCIS-Mi tumors tended to exhibit the highest proportion of HER2 positivity (29.6% for DCIS, 45.0% for DCIS-Mi and 12.4% for IDC-T1, *P*<0.001, **Table 1**). Additionally, the Ki-67 index was higher in IDC-T1 than in pure DCIS or DCIS-Mi.

Based on the treatment strategy, the decision to administer adjuvant endocrine therapy (tamoxifen and/or an aromatase inhibitor) was made by medical oncologists based on the ER and PR expression levels. A total of 75 patients in the DCIS-Mi group were treated with surgery alone (7 for breast-conserving and 68 for mastectomy, **Table 2**). A large proportion of patients with microinvasion preferred to choose adjuvant therapy after surgery. Regarding adjuvant treatment, 131 (54.1%) patients received post-mastectomy chemotherapy.

Disease free survival and breast cancer specific survival

A total of 64 DFS events occurred over a median follow-up of 109 months (range 6-205 months). The 5-year DFS of patients with pure DCIS, DCIS-Mi, and IDC-T1 was 100%, 96.89% and 87.86%, respectively (*P*<0.001, **Figure 1A**). Patients with DCIS-Mi had worse DFS than the DCIS patients (*P*=0.027) but better survival than the IDC-T1 patients (*P*=0.002, **Figure 1A**). In the DCIS-Mi cohort, 17 DFS events occurred during follow-up, including 3 ipsilateral recurrences (all for breast-conserving) and 14 cases of distant metastasis (9 lung, 2 bone and 3 liver). Of the patients who experienced ipsilateral recurrence or metastasis, 13 had received chemotherapy. Regarding the breast cancer specific survival, 5 breast cancer-related deaths occurred among the DCIS-Mi patients, and the 5-year survival was comparable across all three groups (100% for DCIS, 99.32% for DCIS-Mi and 95.42% for IDC-T1, *P*=0.001, **Figure 1B**).

To identify independent prognostic factors for DFS in the DCIS-Mi patients, both univariate

Table 3. Univariate and Multivariate prognostic analysis of DFS for DCIS-Mi patients

Characteristics	Univariate	*P*-value	Multivariate	*P*-value
	HR (95% CI)		HR (95% CI)	
Age (yrs.)		0.74		
Age <50	1 [Reference]			
Age ≥50	0.84 (0.31-2.29)			
Tumor size (cm)		<0.001*		<0.001*
T≤5	1 [Reference]		1 [Reference]	
T>5	19.19 (6.50-56.64)		18.31 (5.53-60.65)	
Lymph node status		0.04*		0.18
Positive	3.67 (1.04-12.96)		1.79 (0.60-15.82)	
Negative	1 [Reference]		1 [Reference]	
Nuclear grade		0.19		
Low-mid	1 [Reference]			
High	2.01 (0.71-5.69)			
Necrosis		0.08		
Yes	3.96 (1.26-12.42)			
No	1 [Reference]			
ER status		0.46		
Positive	0.66 (0.24-1.82)			
Negative	1 [Reference]			
PR status		0.61		
Positive	1.30 (0.48-3.49)			
Negative	1 [Reference]			
HER2 status		0.27		
Positive	0.53 (0.17-1.65)			
Negative	1 [Reference]			
Ki-67 index		0.85		
Ki-67 ≤14	1 [Reference]			
Ki-67 >14	0.91 (0.33-2.47)			
Chemotherapy		0.75		
No	1 [Reference]			
Yes	0.83 (0.27-2.59)			
Radiotherapy		0.005*		0.86
No	1 [Reference]		1 [Reference]	
Yes	4.68 (1.61-13.63)		1.13 (0.27-4.77)	
Endocrine therapy		0.82		
No	1 [Reference]			
Yes	0.89 (0.33-2.38)			
Targeted therapy (Trastuzamab)		0.84		
No	1 [Reference]			
Yes	1.24 (0.16-9.40)			
Therapeutic schemes				
Mastectomy	1 [Reference]	0.63		
Mastectomy + Chemotherapy	1.50 (0.29-7.87)			

DCIS-Mi, ductal carcinoma *in situ* with microinvasion; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; DFS, disease free survival. *Statistically significant.

and multivariate analyses were conducted. In the univariate model, a large tumor size (*P*< 0.001, HR=19.19, 95% CI 6.50-56.64, **Table 3**; **Figure 2**), lymph node involvement (*P*=0.04,

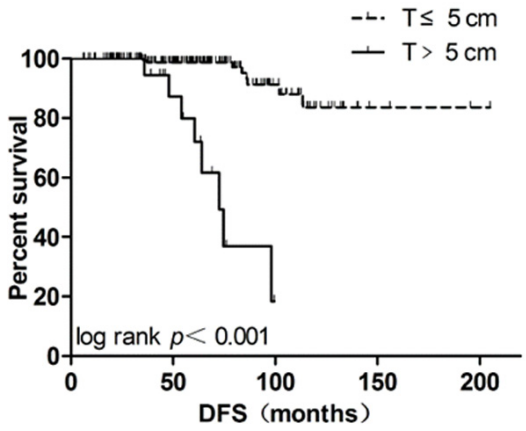

Figure 2. DFS of DCIS-Mi by tumor size (log-rank *P*<0.0001).

HR=3.67, 95% CI 1.04-12.96) and radiotherapy (*P*=0.005, HR=4.68, 95% CI 1.61-13.63) were significantly associated with worse DFS. Other clinicopathological characteristics, including necrosis, the ER, PR, and HER2 statuses, the Ki-67 index, and the nuclear grade, had no significant association with the recurrence or metastasis of DCIS-Mi (**Table 3**). Tumor size, lymph node status, and radiotherapy were included in the multivariate analysis. Only the tumor size was an independent prognostic factor for worse DFS (*P*<0.001, HR=18.31, 95% CI 5.53-60.65).

To elucidate the natural history of DCIS-Mi, we excluded patients treated with chemotherapy, radiation therapy and targeted therapy and reconducted the survival analysis. In the remaining 65 patients, we did not find any clinical characteristics associated with worse DFS (Supplementary Table 1).

Additionally, tumor size (*P*=0.003, HR=15.63, 95% CI 2.53-96.60, **Table 4**), lymph node involvement (*P*=0.01, HR=10.32, 95% CI 1.71-62.32) and radiotherapy (*P*=0.007, HR=11.99, 95% CI 1.99-72.10) were important risk factors for death from breast cancer following a DCIS-Mi diagnosis. Tumor size, lymph node status, and radiotherapy were included in the multivariate analysis. Only the tumor size was an independent prognostic factor for breast cancer specific survival (*P*=0.02, HR=10.88, 95% CI 1.46-81.1).

Chemotherapy effect

As shown in **Table 3**, we found that patients with DCIS-Mi did not benefit from chemotherapy treatment after mastectomy (*P*=0.63, HR=1.50, 95% CI 0.29-7.87). To avoid interference from other factors, we only included patients treated with mastectomy alone or with mastectomy plus adjuvant chemotherapy to explore the effect of chemotherapy.

In the 242 DCIS-Mi cases, 68 patients (28.1%) underwent mastectomy alone, and 131 (54.1%) patients underwent mastectomy followed by adjuvant chemotherapy. The two subgroups differed in age, lymph node status and PR status (Supplementary Table 2). We used Propensity score matching (PSM) to match these features and eliminate potential discrepancies due to these factors. The survival results showed that the risk of ipsilateral recurrence or metastasis for patients receiving mastectomy followed by chemotherapy was not lower than the risk for the patients receiving treatment with mastectomy alone (*P*=0.67, **Figure 3**).

Discussion

Early data indicated that patients with microinvasive carcinomas often had a favorable prognosis. However, due to the paucity and the nonuniformity of clinical outcome data for DCIS-Mi, whether this special type of breast cancer represents a distinct morphological entity with its own biological features and clinical behavior distinct from those of DCIS and IDC remains unclear. To the best of our knowledge, this study is the largest series reported with the longest median follow-up time (109 months) in China. Previous studies have reported conflicting results regarding the survival outcomes of DCIS-Mi patients. Some studies indicated similar survival for DCIS and DCIS-Mi patients, whereas others did not (**Table 5**) [6-8, 10, 11]. With a relatively large sample size, our study indicated that DCIS-Mi exhibited more aggressive biology than DCIS.

Compared with DCIS, DCIS-Mi was associated with a larger tumor size, higher nuclear grade, and more necrosis. Approximately half of the DCIS-Mi tumors were ER- and/or PR-positive, which was similar to the findings in other studies [4, 7, 11]. In pure DCIS, the proportions of ER-positive and PR-positive tumors were 70.0% and 61.4%, respectively, which were slightly higher than the proportion in DCIS-Mi. Notably, HER2 overexpression was significantly more frequent in DCIS-Mi (45.0%) than in DCIS (29.6%) and IDC-T1 (12.4%). Additionally, the

Table 4. Univariate and Multivariate prognostic analysis of breast cancer specific survival for all DCIS-Mi patients

Characteristics	Univariate	*P*-value	Multivariate	*P*-value
	HR (95% CI)		HR (95% CI)	
Age (yrs.)		0.28		
Age <50	1 [Reference]			
Age ≥50	0.30 (0.03-2.66)			
Tumor size (cm)		0.003*		0.02*
T≤5	1 [Reference]		1 [Reference]	
T>5	15.63 (2.53-96.60)		10.88 (1.46-81.1)	
Lymph node status		0.01*		0.318
Positive	10.32 (1.71-62.32)		3.33 (0.31-35.43)	
Negative	1 [Reference]		1 [Reference]	
Nuclear grade		0.22		
Low-Mid	1 [Reference]			
High	4.01 (0.44-36.25)			
Necrosis		0.29		
Yes	2.79 (0.43-18.28)			
No	1 [Reference]			
ER status		0.62		
Positive	1.57 (0.26-9.43)			
Negative	1 [Reference]			
PR status		0.22		
Positive	3.91 (0.44-35.06)			
Negative	1 [Reference]			
HER2 status		0.42		
Positive	0.40 (0.05-3.62)			
Negative	1 [Reference]			
Ki-67 index		0.50		
Ki-67 ≤14	1 [Reference]			
Ki-67 >14	1.86 (0.3-11.55)			
Chemotherapy		0.310		
No	1 [Reference]			
Yes	0.40 (0.07-2.38)			
Radiotherapy		0.007*		0.25
No	1 [Reference]		1 [Reference]	
Yes	11.99 (1.99-72.10)		4.0 (0.38-42.595)	
Endocrine therapy		0.72		
No	1 [Reference]			
Yes	1.39 (0.23-8.33)			
Therapeutic schemes				
Mastectomy	-	(2 cases)		
Mastectomy + Chemotherapy	-			

DCIS-Mi, ductal carcinoma *in situ* with microinvasion; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2. *Statistically significant.

Ki-67 index was higher in IDC-T1 than in DCIS-Mi and DCIS. In our analysis, we found that 8.3% of patients with DCIS-Mi had metastases to the axillary lymph nodes. A similar frequency of lymph node metastasis was reported in a meta-analysis of sentinel lymph node biopsies

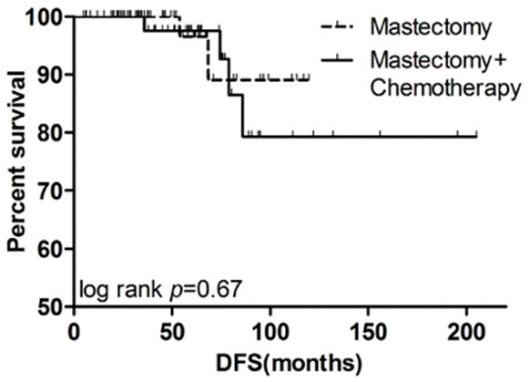

Figure 3. DFS of two different treatments (mastectomy alone and mastectomy + chemotherapy) for DCIS-Mi (log-rank *P*=0.67).

in patients with DCIS-Mi [12]. According to these data, DCIS-Mi has more aggressive pathological factors than DCIS. This phenomenon suggests the natural history of cancer cell progression from DCIS to DCIS-Mi and finally to IDC. This progression also observed at the genetic level: genomic alterations synchronous DCIS genomes were closer to IDC than pure DCIS [13].

The AJCC staging system suggests that pathologists should attempt to quantify the size of lesions in DCIS-Mi. We found that patients with large tumors had worse survival and that tumor size was the most important risk factor for recurrence or distant metastasis in DCIS-Mi. Other clinical, pathological and immunohistochemical features, such as the nuclear grade and ER, PR and HER2 statuses, were not significantly associated with recurrence or distant metastasis in DCIS-Mi, which was similar to a report by Shatat L et al. [14]. However, Fang Yan et al. found that patients with HER2-positive DCIS-Mi had worse survival [8]. In our study, HER2 overexpression, which was highly prevalent, was not significantly associated with recurrence or distant metastasis.

The role of axillary staging in DCIS-Mi remains poorly defined, with the frequency of axillary metastases ranging from 0% to 11% [14-17]. We found an association with recurrence and nodal metastasis in our series, although this factor was not an independent prognostic factor. In our data, patients with IDC-T1, with much more axillary metastases, had a worse prognosis than DCIS-Mi. Although lymph node metastasis may be uncommon in DCIS-Mi patients, it may have an important impact on patient outcomes.

In clinical practice, doctors in China usually suggest the patients with DCIS-Mi to adopt the lumpectomy according to The National Comprehensive Cancer Network Guidelines® for breast cancer (V2.2017). However, most patients in China prefer to mastectomy rather than lumpectomy, because they think mastectomy is much safer for them to avoid local recurrence or metastasis. Doctors gave greater weight to patients' wishes in a more formal sense than ever before. Also, the guideline suggested that patients with microinvasive cancer should be considered for adjuvant chemotherapy according to the hormone receptor, HER2 and lymph node statuses. The therapeutic schemes for DCIS-Mi were similar to those for early-stage invasive breast cancer. In China, in accordance with the guideline, comprehensive consideration of the size of the tumor, necrosis or not, patient's physical condition and other factors, the most effective treatment of microinvasive cancer is the combination of surgical treatment combined with radiotherapy and chemotherapy [18, 19]. Yong C [19] pointed out that the effect of conventional chemotherapy after resection of early breast cancer was better, and the 5-year survival rate of breast cancer patients after surgical excision is 60%. To date, no standard recommendation for the application of chemotherapy and targeted therapy is available for DCIS-Mi patients specifically. The use of chemotherapy and trastuzumab increased among patients with DCIS-Mi after the report of a pivotal trial of trastuzumab in patients with small, node-negative, HER2-positive breast cancer [20]. Our data showed that approximately 68.2% DCIS-Mi patients received adjuvant chemotherapy. However, questions remain concerning whether chemotherapy is beneficial for the patients or represents overtreatment.

To investigate whether post-mastectomy chemotherapy was more beneficial for patients with DCIS-Mi, we matched the clinical and pathological features of two subgroups of patients who underwent mastectomy alone or mastectomy followed by adjuvant chemotherapy. In this analysis, post-mastectomy chemotherapy did not extend the duration of DFS. Therefore, we suspected that post-mastectomy chemotherapy was not necessary for DCIS-Mi patients. Moreover, we conducted a survival analysis

Table 5. Published studies of clinical outcome of DCIS-Mi using the AJCC definition of microinvasion†

Study	Institution	No. of DCIS-Mi patients	Median follow-up	DFS rate	OS rate
Fang Y, 2016 [8]	Shanghai Jiaotong University School of Medicine	84	31 mo.	3-year 89.5%	3-year 100%
Matsen CB, 2014 [10]	Memorial Sloan Kettering Cancer Center	414	59 mo.	5-year 95.9%	5-year 98.3%
Margalit DN, 2013 [7]	Harvard	83	76 mo.	5-year 90.7%	-
Parikh RR, 2012 [6]	Yale	72	107 mo.	10-year 90.7%	95.7%
Vieira CC, 2010 [11]	New York University	21	36 mo. (mean)	100%	100%

DCIS-Mi, ductal carcinoma *in situ* with microinvasion; DFS, disease free survival; OS, overall survival. †AJCC 7th edition, invasive carcinoma no larger than 1 mm.

of patients who did not receive any adjuvant therapy (chemotherapy, radiation therapy or trastuzumab) and did not identify any clinical characteristics associated with worse DFS. With the development of genomics, more guidelines recommend the use of 21-gene Oncotype Dx® to predict benefits from chemotherapy for invasive breast cancer. Other features of tumor progression and the genetic profile may be helpful in predicting the prognosis of DCIS-Mi patients and guiding treatment.

In our cohort, the mortality rate from breast cancer in women with DCIS-Mi is low. Five patients died of breast cancer over a median follow-up of 109 months (range 6-205 months). Therefore, a study following a large cohort for an extended period is necessary to generate a precise estimate of mortality (death from breast cancer after DCIS-Mi is too rare to use as an end point in randomized clinical trials).

Conclusions

This study featured long-term follow-up with a large sample size and matched control populations including patients with DCIS and IDC-T1 to delineate the clinical behavior of DCIS-Mi.

To our knowledge, this is the largest follow-up cohort study on Chinese DCIS-Mi patients. Our data suggest that DCIS-Mi exhibits worse clinical outcome than pure DCIS but better than that of IDC-T1. Tumor size was an independent prognostic factor. Post-mastectomy chemotherapy did not help for increasing DFS for the DCIS-Mi patients. Development of a better algorithm to identify a "chemotherapy beneficial" subgroup for chemotherapy may need to increase the overall survival for DCIS-Mi patients.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Univariate prognostic analysis of DFS for adjuvant therapy-naïve DCIS-Mi patients

Characteristics	Univariate	*P*-value
	HR (95% CI)	
Age (yrs.)		0.23
Age <50	1 [Reference]	
Age ≥50	1.75 (0.18-17.07)	
Tumor size (cm)		0.24
T≤5	1 [Reference]	
T>5	4.31 (0.38-48.46)	
Lymph node status		(1 case)
Positive	-	
Negative	-	
Nuclear grade		0.62
Low-Mid	1 [Reference]	
High	1.92 (0.15-24.88)	
Necrosis		0.36
Yes	3.36 (0.24-51.49)	
No	1 [Reference]	
ER status		0.14
Positive	0.18 (0.02-1.78)	
Negative	1 [Reference]	
PR status		0.19
Positive	0.19 (0.02-2.32)	
Negative	1 [Reference]	
HER2 status		0.64
Positive	1.78 (0.16-20.21)	
Negative	1 [Reference]	
Ki-67 index		0.93
Ki-67 ≤14	1 [Reference]	
Ki-67 >14	1.1 (0.14-8.61)	
Breast surgery		0.10
Mastectomy	0.17 (0.02-1.41)	
Breast-conserving	1 [Reference]	

DCIS-Mi, Ductal carcinoma *in situ* with microinvasion; ER, Estrogen receptor; PR, Progesterone receptor; HER2, Human epidermal growth factor receptor 2; DFS, Disease-free survival.

Supplementary Table 2. Comparison of clinicopathological characteristics from two subgroups of DCIS-Mi

Characteristics	Mastectomy N=68 (%)	Mastectomy + chemotherapy N=131 (%)	*P*-value
Age (yrs.)			0.004*
Age <50	28 (41.2)	82 (62.6)	
Age ≥50	40 (58.8)	49 (37.4)	
Tumor size (cm)			0.5
T≤2	27 (39.7)	63 (48.1)	
2<T≤5	34 (50.0)	58 (44.3)	
T>5	7 (10.3)	10 (7.6)	
Nuclear grade			0.086
Low	1 (1.5)	13 (9.9)	
Mid	18 (26.5)	31 (23.7)	
High	49 (72.1)	87 (66.4)	
Necrosis			0.598
Yes	39 (57.4)	70 (53.4)	
No	29 (42.6)	61 (46.6)	
Lymph node status			0.019*
Negative	68 (100)	121 (92.4)	
Positive	0	10 (7.6)	
ER status			0.144
Negative	31 (45.6)	74 (56.5)	
Positive	37 (54.4)	57 (43.5)	
PR status			0.023*
Negative	30 (44.1)	80 (61.1)	
Positive	38 (55.9)	51 (38.9)	
HER2 status			0.19
0, 1+	24 (35.3)	40 (30.5)	
2+	18 (26.5)	24 (18.3)	
3+	26 (38.2)	67 (51.1)	
Ki-67 index			0.989
Ki-67 ≤14	29 (42.6)	56 (42.7)	
Ki-67 >14	39 (57.4)	75 (57.3)	

DCIS-Mi, Ductal carcinoma *in situ* with microinvasion; ER, Estrogen receptor; PR, Progesterone receptor; HER2, Human epidermal growth factor receptor 2. *Statistically significant.