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RESEARCH ARTICLE

Clinicopathologic characteristics and molecular subtypes of microinvasive carcinoma of the breast

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Abstract Patients with microinvasive carcinoma often have favorable prognosis, but it remains unclear whether this special type of breast cancer represents a distinct morphological entity with its own biological features and clinical behavior distinct from those of ductal carcinoma in situ (DCIS). The study is a retrospective analysis of a large patient cohort from a single institution. One hundred and thirty one microinvasive carcinoma and 451 DCIS cases were collected. ER, PR, HER2, and Ki67 were examined by immunohistochemistry in pathological sections. We assessed the clinicopathologic characteristics, molecular features, and survival status of microinvasive carcinoma and compared to those of DCIS. Microinvasive carcinoma differed from DCIS with respect to tumor size, lymph node status, and initial presentation ($P<0.05$). There was a significant difference in nuclear grade among microinvasive carcinoma of different molecular subtype ($P<0.05$). The clinicalpathologic features and outcomes of patients with microinvasive carcinoma were similar to those with DCIS. The 5-year OS rate for microinvasive carcinoma and DCIS patients was 99.0 and 99.2 %, respectively. A combination of pathologic, clinical, and molecular factors may ultimately reveal more powerful and robust measures for disease classification than any one modality alone. Microinvasive carcinoma does not significantly predict for worse DFS or OS in comparison with patients with DCIS.

Keywords Breast cancer · Microinvasive carcinoma · Pathological features · Molecular subtypes · Prognosis

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Introduction

Breast cancer is one of the most common cancers and the second highest cancer-related cause of death among women [1]. Ductal carcinoma in situ (DCIS) accounts for about 25 % of newly diagnosed breast cancer cases in the USA, and approximately 10 to 15 % of breast cancers detected by mammography in China [2]. Recent data suggests that microinvasive carcinoma is the interim stage in the progression from DCIS to invasive breast cancer [3, 4]. It possesses potential for invasion and metastasis and requires different surgical strategy compared to DCIS [5].

Microinvasive carcinoma is uncommon, accounting for less than 1 % of all breast cancers [6]. Lagios in 1982 introduced the term “microinvasion” in breast pathology as synonymous of invasion less than 1 mm [7]. Ellis et al. recommended that microinvasive carcinoma is a tumor in which the dominant lesion is non-invasive, but in which there are one or more clearly separate small, microscopic foci of infiltration into non-specialized interlobular stroma [8]. Alternatively, microinvasive carcinoma had different definitions ranging from 1 to 2 mm in diameter [6, 9], with other differentiating microinvasion into single cell and cell clusters [3]. The WHO definition of a lesion characterized by one or more clearly separate microscopic foci of infiltration of tumor cells into the mammary stroma, each less than or equal to 1 mm in size, and most commonly seen in the background of high-grade DCIS [10] was adopted in this study. Immunohistochemistry (IHC)

may be of value in distinguishing microinvasion from its mimics (Fig. 1).

Some authors considered microinvasive carcinoma with its potential for metastasis to represent a distinct entity, with features different than those seen in pure DCIS [6]. DCIS can be classified into the same major molecular subtypes identified in invasive breast cancer using IHC as follows: Luminal A, Luminal B/HER2 negative, Luminal B/HER2 positive, HER2 enriched, and Triple negative breast cancers (TNBCs) [11, 12]. Although several authors have reported on the clinical presentation and histopathologic findings of microinvasive carcinoma, the IHC features have not been well described, and these may represent significant prognostic indicator for recurrence. Thus, this study was carried out to evaluate the clinicopathologic features, such as clinical presentation, histopathology findings, IHC marker-based subtyping, and clinical outcome of patients diagnosed with microinvasive carcinoma.

Materials and methods

Patients' characteristics

The cohort included all cases diagnosed with microinvasive carcinoma and DCIS collected from the Tianjin Medical University Cancer Institute and Hospital between 21 February 2002 and 23 December 2009. This was a well-characterized series of patients who had undergone long-term follow-up organized by a single institution. In microinvasive carcinoma

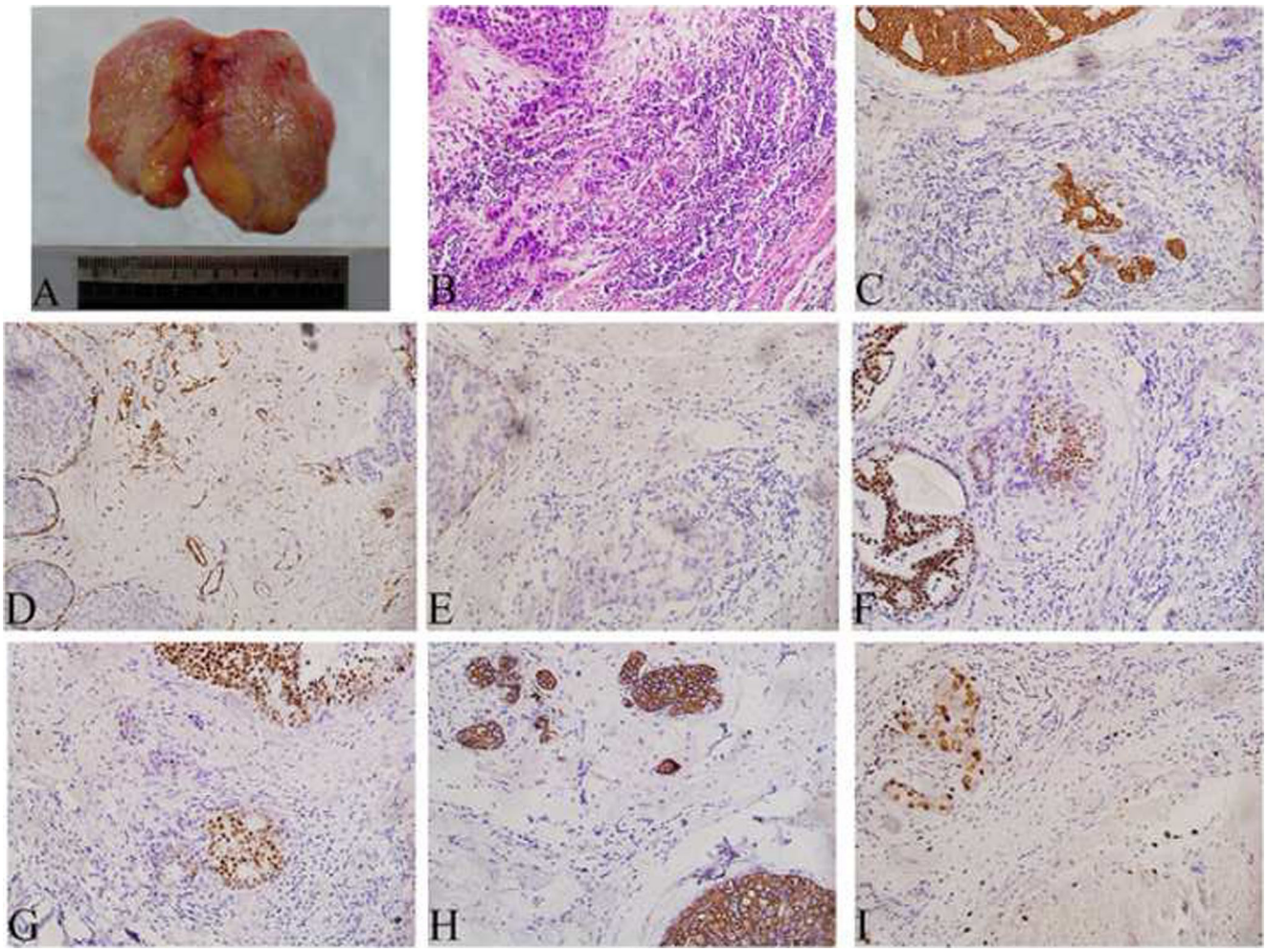

Fig. 1 **a** Specimen edge is ill defined and lacks sharp circumscription. The tumor is hard during palpation. The cut surface is grey-white, comedo type. **b** Microinvasive carcinoma of the breast. HE staining; ×200 magnification. Small invasive cell clusters within stromal spaces distributed over a 0.40 mm area and surrounded by a dense lymphocytic infiltrate. **c** Stains for CK highlight the microinvasive foci and complement stains for myoepithelial cells; ×200 magnification. **d** Immunostain for SMA decorates the vessel walls and myoepithelial layer of DCIS, while absence of myoepithelial cells around the tumor cell clusters confirms their invasive nature; ×200 magnification. **e** IHC staining is negative for calponin; ×200 magnification. **f** IHC staining of ER revealed nuclear staining; ×200 magnification. **g** IHC staining of PR revealed nuclear staining; ×200 magnification. **h** The tumor showed strong membrane staining of HER2; ×200 magnification. **i** IHC staining of Ki67 revealed nuclear staining; ×200 magnification

cases, all the patients underwent preoperative mammography and ultrasound of the breast. The entire samples were exhaustively examined so as not to miss small foci of invasive carcinoma, particularly in the setting of extensive in situ carcinoma. Microinvasive carcinoma was defined using the WHO definition [10]. All patients involved in this study had the diagnosis of microinvasive carcinoma confirmed by two of the authors.

All patients underwent local and/or systemic treatments. Local treatment included surgery and radiotherapy. Surgical procedures consisted of mastectomy and breast-conserving surgery. Patients who underwent breast-conserving surgery had adjuvant radiotherapy routinely. Systemic treatments included chemotherapy and endocrine therapy. Chemotherapy was only given in cases with nodal disease. All the patients were treated according to National Comprehensive Cancer Network (NCCN) guidelines.

Clinicopathological evaluation

In all cases, the following clinical information was obtained: patients' demographics (age, menopausal status, and family history), tumor characteristics (nuclear grade, size, LN status, and subtype), type of adjuvant systemic treatment (chemotherapy, radiotherapy, and endocrine therapy), and recurrence and survival information. The tumors were nuclear graded as low, intermediate, and high basing on hyperchromasia, pleomorphism, and nuclear to cytoplasmic ratio. Initial presentation included clinical and radiological presentations. Clinical presentation included symptomatology of mass or nipple discharge, while radiological presentation was detected by mammographic changes. Patients who were treated before June 2013 were followed for outcome data including overall survival (OS) time and disease-free survival (DFS) time. The study protocol was approved by the Human Ethical Committee of Tianjin Medical University Cancer Institute and Hospital. Informed consent was obtained from all patients before their surgery and before the examination of the specimens.

IHC assay and evaluation of the staining

The IHC was performed on formalin-fixed, paraffin-embedded samples obtained from the pathology registry. Tissue sections (5 μm) were deparaffinized in xylene and rehydrated in a graded series of ethanol. The slides were treated with methanol containing 0.3 % hydrogen peroxide to block any endogenous peroxidase activity. Heat-mediated antigen retrieval with the pressure cooker method was used for all staining. Estrogen receptor (ER) (SP1, 1:200 dilution; ZETA), progesterone receptor (PR) (SP2, 1:200 dilution; ZETA), HER2 (CB11, 1:100 dilution; Invitrogen), and Ki67 (K-2, 1:100 dilution; Invitrogen) antibodies were used for IHC studies on serial tissue sections from each case.

The immunostaining was scored by two authors blinded to patients' clinicopathologic characteristics and outcome. For each antibody, the location of immunoreactivity, percentage of stained cells, and intensity were determined. The final score on the percentage and intensity was taken from the mean scores for each observer. ER and PR were considered positive if nuclear staining was present in more than 1 % of the tumor cells, HER2 was considered positive when there was a strong whole membrane staining in >10 % of the tumor cells, and Ki67 was expressed as percentage of positive cells (strong nuclear staining), with a threshold of 20 % or above being considered high. In addition, ER and PR status was determined for both the invasive and in situ components of the microinvasive carcinoma, while HER2 expression was determined only in the invasive component of the microinvasive carcinoma.

The cases were also classified into intrinsic subtypes using IHC surrogate as follows [12]:

Luminal A hormone receptor (HR) positive, HER2 negative, and low (<20 %) Ki67 labeling index (LI);
Luminal B/HER2 negative, HR positive, HER2 negative, and high (≥20 %) Ki67 LI;
Luminal B/HER2 positive, HR positive, and HER2 positive;
HER2 enriched HR negative and HER2 positive;
TNBCs HR negative and HER2 negative.

Statistics

Statistical analysis was carried out using SPSS software (Version 17.0 for Windows). The correlation analyses between the immunophenotype and the various clinicopathologic and biological factors were examined by the χ^2 test. OS and DFS were conducted using the Kaplan–Meier curves. $P<0.05$ was considered statistically significant.

Results

Patient cohort

This study included 131 microinvasive carcinoma and 451 DCIS. The median age of microinvasive carcinoma patients was 49 years (range 24–86 years). The clinicopathologic features are shown in Table 1. There was a significant difference in clinical tumor size, LN status, and initial presentation ($P<0.05$) between microinvasive carcinoma and DCIS. Aggressive features like larger tumor size and more LN metastases were associated with microinvasive carcinoma. There was no distinguished difference in age, nuclear grade, menopausal

Table 1 Patients' demographics and clinicopathologic characteristics of microinvasive carcinoma compared with DCIS

Characteristic	Microinvasive carcinoma (n=131)		DCIS (n=451)		χ^2	P values
	Number	%	Number	%		
Age at diagnosis (years)						
<40	25	19.1	69	15.3	3.801	0.284
40–55	73	55.7	240	53.2		
56–70	30	22.9	116	25.7		
>70	3	2.3	26	5.8		
Tumor size (cm)						
≤2	48	36.6	224	49.7	7.345	0.025
2–5	75	57.3	210	46.6		
>5	8	6.1	17	3.8		
Nuclear grade						
1	41	31.3	174	38.6	2.329	0.312
2	64	48.9	195	43.2		
3	26	19.8	82	18.2		
Lymph node status						
0	121	92.4	447	99.1	20.186	0.000
1–3	9	6.9	4	0.9		
4–9	1	0.8	0	0.0		
≥10	0	0.0	0	0.0		
Menopausal status						
Premenopausal	81	61.8	259	57.4	0.811	0.368
Postmenopausal	50	38.2	192	42.6		
Family history						
No	118	90.1	422	93.6	1.85	0.174
Yes	13	9.9	29	6.4		
Initial presentation						
Clinical	46	35.1	232	51.4	10.846	0.001
Radiologic	85	64.9	219	48.6		
Endocrine therapy						
No	63	48.1	178	39.5	3.112	0.078
Yes	68	51.9	273	60.5		
ER status						
Negative	49	37.4	154	34.1	0.474	0.491
Positive	82	62.6	297	65.9		
PR status						
Negative	55	42.0	175	38.8	0.430	0.512
Positive	76	58.0	276	61.2		
Her-2						
Negative	63	48.1	188	41.7	1.699	0.192
Positive	68	51.9	263	58.3		
ki67						
<20	40	30.5	160	35.5	1.099	0.294
≥20	91	69.5	291	64.5		
Subtype						
Luminal A	20	15.3	65	14.4	3.184	0.528
Luminal B(Her2−)	34	26.0	100	22.2		
Luminal B(Her2+)	43	32.8	185	41.0		
Her-2	25	19.1	78	17.3		
Triple-negative	9	6.9	23	5.1		

status, family history, endocrine therapy, hormone receptors, or subtype (P≥0.05) between the two groups.

Molecular immunophenotype

Of the 131 microinvasive carcinoma, 20 (15.3 %) were luminal A, 34 (26.0 %) were luminal B (HER2−), 43 (32.8 %) were luminal B (HER2+), 25 (19.1 %) were HER2-enriched, and 9 (6.9 %) were TNBCs. The clinicopathological characteristics among these subtypes were compared (Table 2). There was a significant difference in nuclear grade among different subtypes (P<0.05). Higher nuclear grade was associated with HER2-enriched and TNBCs. There was no difference in age, tumor size, lymph node status, menopausal status, or family history (P≥0.05) among the different subtypes.

Of the 451 DCIS, 65 (14.4 %) were luminal A, 100 (22.2 %) were luminal B (HER2−), 185 (41.0 %) were luminal B (HER2+), 78 (17.3 %) were HER2-enriched, and 23 (5.1 %) were TNBCs. The clinicopathological characteristics among these subtypes were compared (Table 3). There were significant differences in age, tumor size, nuclear grade, and menopausal status among different subtypes (P<0.05). Older patients, larger tumor size, higher nuclear grade, and postmenopausal status were associated with HER2-enriched and TNBCs in DCIS. There was no difference in lymph node status or family history (P≥0.05).

Disease-specific outcomes

The 5-year OS rates for microinvasive carcinoma and DCIS patients were 99.0 and 99.2 %, respectively. The 5-year DFS rates for microinvasive carcinoma and DCIS patients were 95.2 and 95.9 %, respectively, with a median follow-up of 69 and 62 months, respectively. There was no difference in outcome in patients with or without microinvasion (Fig. 2a, b).

Discussion

In this study, there was a significant difference in tumor size, LN status, initial presentation, and HER2 expression between patients with microinvasive carcinoma or DCIS, but there was no difference in age, nuclear grade, menopausal status, family history, endocrine therapy, hormone receptors, or intrinsic subtypes.

Most (80 %) cases are non-palpable and are diagnosed by mammography alone [13]. However, in up to 24 % over-diagnosis of screen-detected cancer has recently been reported [14]. When there is doubt about the diagnosis of microinvasive carcinoma or if the suspicious area is no longer seen on further sections, a diagnosis of in situ lesion with no

Table 2 Distribution of clinicopathological characteristics among microinvasive carcinoma intrinsic subtypes

Characteristic	Luminal A (n=20)		Luminal B(HER2−) (n=34)		Luminal B(HER2+) (n=43)		HER2 (n=25)		Triple-negative (n=9)		χ^2	P values
	Number	%	Number	%	Number	%	Number	%	Number	%		
Age at diagnosis (years)												
<35	2	10.0	3	8.8	2	4.7	1	4.0	0	0.0	14.267	0.284
35–50	14	70.0	22	64.7	21	48.8	13	52.0	3	33.3		
51–70	4	20.0	9	26.5	18	41.9	11	44.0	5	55.6		
>70	0	0.0	0	0.0	2	4.7	0	0.0	1	11.1		
Tumor size (cm)												
≤2	11	55.0	13	38.2	12	27.9	8	32.0	4	44.4	7.589	0.475
2–5	7	35.0	20	58.8	29	67.4	15	60.0	4	44.4		
>5	2	10.0	1	2.9	2	4.7	2	8.0	1	11.1		
Nuclear grade												
1	14	70.0	14	41.2	10	23.3	1	4.0	2	22.2	37.614	0.000
2	4	20.0	16	47.1	28	65.1	13	52.0	3	33.3		
3	2	10.0	4	11.8	5	11.6	11	44.0	4	44.4		
Lymph node status												
0	20	100.0	32	94.1	40	93.0	21	84.0	8	88.9	7.197	0.516
1–3	0	0.0	2	5.9	3	7.0	3	12.0	1	11.1		
4–9	0	0.0	0	0.0	0	0.0	1	4.0	0	0.0		
≥10	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
Menopausal status												
Premenopausal	16	80.0	24	70.6	24	55.8	13	52.0	4	44.4	6.739	0.150
Postmenopausal	4	20.0	10	29.4	19	44.2	12	48.0	5	55.6		
Family history												
No	19	95.0	29	85.3	38	88.4	24	96.0	8	88.9	2.548	0.636
Yes	1	5.0	5	14.7	5	11.6	1	4.0	1	11.1		

definite evidence of established microinvasive carcinoma should be rendered. Microinvasion can also be underdiagnosed because of sampling issues, as microinvasive carcinoma cannot be reliably excluded unless all tissue is serially sectioned and sequentially submitted for histologic examination, which is recommended in clinical guidelines [15].

ER and PR expression is routinely evaluated in all DCIS for management planning. They are more frequently expressed in low-grade than high-grade DCIS, and their expression is associated with a lower risk of local recurrence [16]. The reported expression rates in DCIS range from 60 to 78 % [17], similar to the current series. Also, this study showed that ER and PR expressions were similar in microinvasive carcinoma and in DCIS, suggesting the hormone receptor status was determined at DCIS stage. Similarly, other markers known to have prognostic and predictive value in the management of invasive breast cancers have been evaluated in DCIS. Rakovitch et al. showed that HER2+ and Ki-67+ DCIS have a higher risk of developing local DCIS recurrence [18]. Interestingly, HER2, which traditionally predicts a more aggressive disease course in invasive breast cancer, is expressed in a greater proportion of DCIS tumors than in invasive cancers [4]; however, there is still a controversy as to whether HER2 positivity may be associated with an increased risk of invasive recurrence [19]. In a single institution review of 103 patients with DCIS, HER2 was overexpressed in 61 % of cases [20]. In contrast, another single institution review of 106 patients with DCIS noted HER2 overexpression in only 37 % of cases [21]. Our study found that HER2 positive expression was 51.9 % in microinvasive carcinoma and 58.3 % in DCIS.

Recently, the use of gene expression microarray technology was resulted in a new classification based on molecular signatures. Similarly, subtypes of DCIS were described with essentially similar distribution pattern [11]. The similar molecular signature subtypes distribution further establishes DCIS as precursors of the different subtypes of invasive breast carcinomas and raises the possibility of innovative prevention strategies in DCIS. Our findings were similar to those reported previously in women of Western countries. The absence of difference in molecular subtype distribution between microinvasive carcinoma and DCIS suggested that molecular subtypes were determined in DCIS stage. Kurbel found DCIS to be steroid receptor positive (around 60 %) or negative (40 %) at initial stage, subsequently some of these DCIS

Table 3 Distribution of clinicopathological characteristics among DCIS intrinsic subtypes

Characteristic	Luminal A (n=65)		Luminal B (HER2−) (n=100)		Luminal B(HER2+) (n=185)		HER2 (n=78)		Triple-negative (n=23)		χ^2	P values
	Number	%	Number	%	Number	%	Number	%	Number	%		
Age at diagnosis (years)												
<35	3	4.6	7	7.0	13	7.0	4	5.1	2	8.7	32.122	0.001
35–50	32	49.2	51	51.0	100	54.1	23	29.5	7	30.4		
51–70	25	38.5	32	32.0	63	34.1	50	64.1	13	56.5		
>70	5	7.7	10	10.0	9	4.9	1	1.3	1	4.3		
Tumor size (cm)												
≤2	43	66.2	55	55.0	85	45.9	31	39.7	10	43.5	18.787	0.016
2–5	22	33.8	44	44.0	89	48.1	44	56.4	11	47.8		
>5	0	0.0	1	1.0	11	5.9	3	3.8	2	8.7		
Nuclear grade												
1	40	61.5	57	57.0	68	36.8	5	6.4	4	17.4	111.380	0.000
2	23	35.4	36	36.0	91	49.2	33	42.3	12	52.2		
3	2	3.1	7	7.0	26	14.1	40	51.3	7	30.4		
Lymph node status												
0	65	100.0	100	100.0	181	97.8	78	100.0	23	100.0	5.803	0.214
1–3	0	0.0	0	0.0	4	2.2	0	0.0	0	0.0		
4–9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
≥10	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
Menopausal status												
Premenopausal	39	60.0	66	66.0	112	60.5	31	39.7	11	47.8	14.759	0.005
Postmenopausal	26	40.0	34	34.0	73	39.5	47	60.3	12	52.2		
Family history												
No	62	95.4	93	93.0	175	94.6	72	92.3	20	87.0	2.611	0.625
Yes	3	4.6	7	7.0	10	5.4	6	7.7	3	13.0		

over-expressed HER2 by epigenetic mechanisms and became either luminal B (20 %) or HER2-enriched (10 %). The remaining DCIS with low HER2 expression become luminal A (40 %) or TNBC DCIS (30 %) [22]. In the progression to invasive breast cancers, TNBCs were most rapid, while the HER2-enriched tumors were almost three times slower. At the time of diagnosis, the proportion of HER2-enriched cancers was higher probably due to their slow progression, while the TNBCs would be almost absent. We found that there were significant differences in nuclear grade among the subtype cohorts (Table 2). Aggressive features like higher nuclear grade were associated with aggressive phenotypes of HER2-

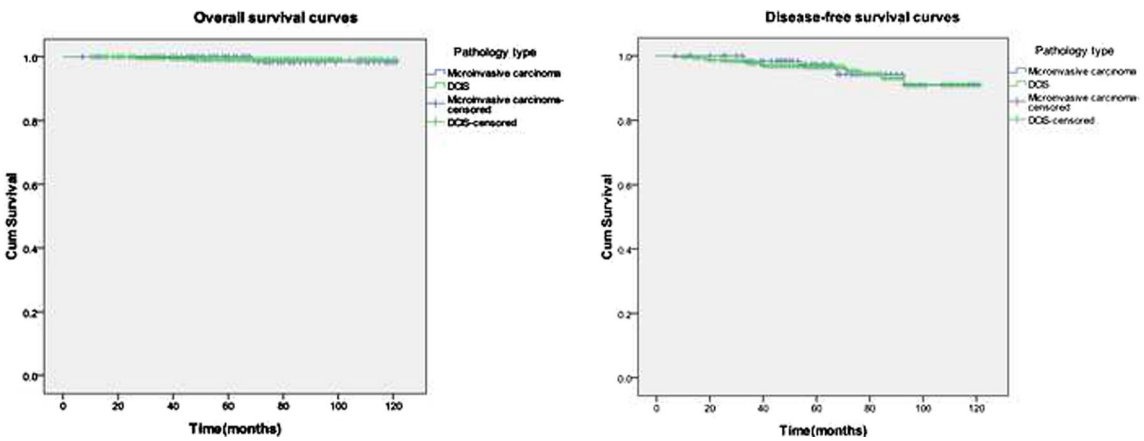

Fig. 2 **a** Kaplan–Meier survival curve showing the comparison of overall survival between microinvasive carcinoma and ductal carcinoma in situ (χ^2=0.003, P=0.957). **b** Kaplan–Meier survival curve showing the comparison of disease-free survival between microinvasive carcinoma and ductal carcinoma in situ (χ^2=0.050, P=0.822)

enriched and TNBCs in microinvasive and DCIS lesions (Table 3).

Patients with DCIS with evidence of widespread disease require a total mastectomy without lymph node dissection. For the vast majority of patients with more limited disease where negative margins are achieved with the initial excision or with re-excision, breast-conserving therapy or total mastectomy is the appropriate treatment options. Although mastectomy provides maximum local control, the long-term, cause-specific survival with mastectomy appears to be equivalent to that with excision and whole breast irradiation [23]. UK, Australia, and New Zealand (UK/ANZ), a major randomized trial evaluating tamoxifen in DCIS demonstrated significant benefit, was observed in the lumpectomy plus tamoxifen alone arm [24]. Many microinvasive carcinoma patients in our study had ER + tumors and thus the use of adjuvant hormonal therapy may be beneficial.

Overall, the 5-year OS rates for microinvasive carcinoma and DCIS patients were 99.0 and 99.2 %, respectively. The 5-year DFS rates for microinvasive carcinoma and DCIS patients were 95.2 and 95.9 %, respectively, with a median follow-up of approximately 5 years. These figures were similar to those reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 prospective study at 8 years [25]. Although some authors suggested that microinvasive carcinoma and DCIS represent a spectrum of breast cancers with a gradient of aggressiveness, our study suggests that a focus of microinvasion of <1 mm in patients with intraductal cancer does not necessarily confer a more unfavorable prognosis and has a natural history that resembles that of pure DCIS.

The strength of the present study was a specific evaluation of the molecular subtypes of the microinvasive breast carcinoma in Chinese women. To our knowledge, it is the largest series reported to date in a Chinese population with a median follow-up of >5 years.

Several limitations in our series should be noted. The decision to undergo therapy was not randomized, but rather driven by physician recommendations and patient preference, which may introduce unmeasured selection bias. Additionally, in our analysis of risk factors for recurrence, we could not perform multivariate analysis because of the small number of events and the potential for statistical overfitting of the model.

In conclusion, the clinicalpathologic features and outcomes of breast cancer patients with microinvasion seem to be equivalent to those with DCIS. The challenge in the future will be to differentiate subtypes of microinvasive carcinoma that had a higher propensity to recur or progress to invasive disease from the more indolent forms of the disease and to tailor treatment decisions accordingly.

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Conflicts of interest None

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64:9–29.
2. Fan L, Zheng Y, Yu KD, Liu GY, Wu J, Lu JS, et al. Breast cancer in a transitional society over 18 years: Trends and present status in Shanghai, China. Breast Cancer Res Treat. 2009;117:409–16.
3. de Mascarel I, MacGrogan G, Mathoulin Pélissier S, Soubeyran I, Picot V, Coindre JM. Breast ductal carcinoma in situ with microinvasion. Cancer. 2002;94:2134–42.
4. Yu KD, Wu LM, Liu GY, Wu J, Di GH, Shen ZZ, et al. Different distribution of breast cancer subtypes in breast ductal carcinoma in situ (DCIS), DCIS with microinvasion, and DCIS with invasion component. Ann Surg Oncol. 2011;18:1342–8.
5. Vieira CC, Mercado CL, Cangiarella JF, Moy L, Toth HK, Guth AA. Microinvasive ductal carcinoma in situ: Clinical presentation, imaging features, pathologic findings, and outcome. Eur J Radiol. 2010;73:102–7.
6. Silver SA, Tavassoli FA. Mammary ductal carcinoma in situ with microinvasion. Cancer. 1998;82:2382–90.
7. Lagios MD, Westdahl PR, Margolin FR, Rose MR. Duct carcinoma in situ. Relationship of extent of noninvasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. Cancer. 1982;50:1309–14.
8. Ellis IO, Tavassoli FA. Microinvasive carcinoma. In: Tavassoli FA, Devilee P, editors. Pathology & genetics: Tumours of the breast and female genital organs. 3rd ed. Lyon: IARC Press; 2003. p. 74–5.
9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17:1471–4.
10. Pinder SE, Ellis IO, Schnitt SJ, Tan PH, Rutgers E, Morrow M. Microinvasive carcinoma. In: Lakhani SR, Ellis IO, Schnitt SJ, editors. WHO classification of tumours of the breast. 4th ed. Lyon: IARC Press; 2012. p. 96–7.
11. Clark S, Warwick J, Carpenter R, Bowen R, Duffy S, Jones J. Molecular subtyping of DCIS: Heterogeneity of breast cancer reflected in pre-invasive disease. Br J Cancer. 2011;104:120–7.
12. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B. Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24:2206–23.
13. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst. 2010;102:170–8.
14. Welch HG, Schwartz LM, Woloshin S. Ramifications of screening for breast cancer: 1 in 4 cancers detected by mammography are pseudocancers. BMJ. 2006;332:727.
15. Olivotto I, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: the management of ductal carcinoma in situ (summary of the 2001 update). C M A J. 2001;165:912–3.
16. Lari SA, Kuerer HM. Biological markers in DCIS and risk of breast recurrence: a systematic review. J Cancer Educ. 2011;2:232.
17. Daly MB. Tamoxifen in ductal carcinoma in situ. Semin Oncol. 2006;33:647–9.
18. Rakovitch E, Nofech-Mozes S, Hanna W, Narod S, Thiruchelvam D, Saskin R, et al. HER2/neu and Ki-67 expression predict non-invasive

recurrence following breast-conserving therapy for ductal carcinoma in situ. Br J Cancer. 2012;106:1160–5.
19. von Minckwitz G, Darb-Esfahani S, Loibl S, Huober J, Tesch H, Solbach C, et al. Responsiveness of adjacent ductal carcinoma in situ and changes in HER2 status after neoadjuvant chemotherapy/trastuzumab treatment in early breast cancer—Results from the GeparQuattro study (GBG 40). Breast Cancer Res Treat. 2012;132:863–70.
20. Horimoto Y, Tokuda E, Arakawa A, Kosaka T, Saito M, Kasumi F. Significance of HER2 protein examination in ductal carcinoma in situ. J Surg Res. 2011;167:e205–10.
21. Roses RE, Paulson EC, Sharma A, Schueller JE, Nisenbaum H, Weinstein S, et al. HER-2/neu overexpression as a predictor for the transition from in situ to invasive breast cancer. Cancer Epidemiol Biomarkers Prev. 2009;18:1386–9.
22. Kurbel S. In search of triple-negative DCIS: tumor-type dependent model of breast cancer progression from DCIS to the invasive cancer. Tumour Biol. 2013;34:1–7.
23. Fisher B, Dignam J, Wolmark N, Mamounas E, Costantino J, Poller W, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol. 1998;16:441–52.
24. Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2011;12:21–9.
25. Lyman GH, Giuliano AE, Somerfield MR, Benson AB, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005;23:7703–20.