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Clinical characteristics of breast ductal carcinoma in situ with microinvasion: a narrative review

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Abstract

Ductal carcinoma in situ (DCIS) with microinvasion (DCIS-MI) is defined as the extension of cancer cells beyond the basement membrane into adjacent tissue with no focus larger than 1 mm or a maximum diameter of less than 1 mm for multiple invasive foci. DCIS-MI constitutes approximately 1% of all breast cancer cases and 5% to 10% of cases of DCIS. The current literature is controversial concerning the clinical prognostic features and management of DCIS-MI. This narrative review described recently reported literature regarding the characteristics, diagnosis, treatment, and prognosis of DCIS-MI.

Introduction

Microinvasive carcinoma constitutes approximately 1% of all breast cancer cases and 5% to 10% of cases of ductal carcinoma in situ (DCIS).[1–3] DCIS is a hyperplastic disease originating from the terminal duct that is limited to the mammary duct.[4] DCIS further develops into invasive ductal carcinoma (IDC) once the tumor breaks through the basement membrane.

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DCIS with microinvasion (DCIS-MI) is the interim stage between DCIS and IDC. DCIS-MI comprises approximately 1% of all cases of breast cancer, and its morbidity is increasing globally.[5] Because a consensus guideline for the diagnosis and treatment of DCIS-MI has not been published, we summarized the history of its diagnosis, prognosis, and treatment and attempted to clarify management options for patients.

Literature search

We searched PubMed for relevant articles covering the period of 1970 to February 2020 using the following terms: DCIS, DCIS-MI, DCIS-IDC, SLNB, and ALND. We reviewed publications retrieved from this search and selected those that were deemed relevant. Valid publications included full-text studies in English involving women diagnosed with primary DCIS, DCIS-MI, and DCIS-IDC. Animal studies, conference abstracts, case reports/case series, commentaries, and letters to the editor were excluded.

Evolution of the definition of DCIS-MI

The definition of DCIS-MI has evolved for some time because of the use of different diagnostic criteria. The early definition of microinvasion in DCIS was the infiltration of tumor cells into the adjacent stroma.[6] However, it was difficult to determine whether the extraductal stroma was accompanied by tumor cell infiltration and clarify the extent of infiltration because of limitations concerning scientific and technological modalities, as well as the influence of inflammatory cell infiltration. Subsequently, several definitions of DCIS-MI were described by scholars.[7–17] In 1997, the fifth edition of the American Joint Committee on Cancer (AJCC) staging system defined microinvasive carcinoma as

breast cancer cells breaking through the basement membrane and entering the adjacent stroma with a maximum invasive focus diameter of no more than 1 mm.[18] This definition has been accepted widely since the seventh edition of the AJCC staging system was released in 2010.[19]

Clinical pathology and prognosis of microinvasion

Clinical pathology of microinvasion

In a study assessing the pathologic characteristics of 810 slides from 801 patients with various stages of ductal carcinoma, there were no significant differences in sex and age among the DCIS, DCIS-MI, and DCIS-IDC groups.[20] The proportions of patients with a high nuclear grade were 40.2% in DCIS, 77.6% in DCIS-MI, and 61.6% in DCIS-IDC ($P < 0.001$). 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. Tumor size was significantly larger in the DCIS-MI and DCIS-IDC groups than in the DCIS group ($P = 0.002$ and $P < 0.001$, respectively). Significant differences were found in the rate of comedo necrosis among the three groups (10.8% in DCIS, 30.7% in DCIS-MI, and 3.7% in DCIS-IDC; $P < 0.05$). The rates of lymph node positivity in the DCIS, DCIS-MI, and DCIS-IDC groups were 0.5%, 13.3%, and 40.3%, respectively, with significant differences among the groups ($P < 0.05$). The rates of estrogen receptor (ER; DCIS, 69.9%; DCIS-MI, 40.5%; DCIS-IDC, 79.0%; $P < 0.05$) and progesterone receptor (PR) positivity (DCIS, 65.7%; DCIS-MI, 44.0%; DCIS-IDC, 75.1%; $P < 0.05$) were significantly different among the groups. DCIS-MI had a significantly higher rate in human epidermal growth factor receptor 2 (HER2) expression than DCIS and DCIS-IDC ($P < 0.05$). The proportions of patients with high Ki-67 indices were 40.5%, 75%,

and 71.7% in the DCIS, DCIS-MI, and DCIS-IDC groups, respectively ($P < 0.05$). Similar findings was reported by Korean scholars,[15] who analyzed 613 cases of DCIS diagnosed in the Affiliated Hospital of Seoul National University from 2003 to 2014, including 136 cases of DCIS-MI and 477 cases of DCIS. As presented in Table 1, tumor diameters exceeding 3.2 cm, high nuclear grades, necrosis, and acne-like structures were associated with higher rates microinvasion ($P < 0.001$). The rates of HER2 and Ki-67 positivity were significantly higher in patients with DCIS-MI than in those with DCIS ($P < 0.001$), whereas the rates of ER and PR positivity were lower in patients with DCIS-MI ($P < 0.001$).

Table 1. Pathological features of patients enrolled in the study.[15]

Characteristic	DCIS N = 477	DCIS-MI N = 136	P
ER			<0.001
Negative	83 (17.4%)	74 (54.4%)	
Positive	394 (82.6%)	62 (45.6%)	
PR			<0.001
Negative	128 (26.8%)	88 (64.7%)	
Positive	349 (73.2%)	48 (35.3%)	
HER2			<0.001
Negative	369 (77.4%)	58 (42.6%)	
ositive	108 (22.6%)	78 (57.4%)	
P53			<0.001
Negative	403 (84.5%)	83 (61.0%)	
Positive	74 (15.5%)	53 (39.0%)	<0.001
Ki-67			
<20	421 (88.3%)	91 (66.9%)	
≥20	56 (11.7%)	45 (33.1%)	
Subtype			<0.001
Luminal A	320 (67.1%)	34 (25.0%)	
Luminal B	77 (16.1%)	30 (22.1%)	
HER2+	51 (10.7%)	55 (40.4%)	
Triple-negative	29 (6.1%)	17 (12.5%)	

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

Clinical prognosis of DCIS-MI

Although the definition of microinvasion in the AJCC 7th edition has been widely used in recent years, different factors such as enrollment conditions, the number of participants, and the follow-up duration resulted in inconsistent results. Some clinical studies suggested that the prognosis of DCIS-MI was similar to that of DCIS, whereas other researchers reported contrary findings. For example, a retrospective clinical study of breast-conserving surgery at Yale University Medical School from 1973 to 2004 included 72 patients with DCIS-MI and 321 patients with DCIS, with all patients receiving local radiotherapy. The regional recurrence rate after 10 years did not differ between the DCIS-MI and DCIS groups (8.3% vs. 6.8%),[21] as detailed in Table 2. Wang et al.[22] enrolled 582 patients from the Cancer Research Institute and Affiliated Hospital of Tianjin Medical University from February 2002 to December 2009, including 131 patients with DCIS-MI and 451 patients with DCIS. The median follow-up duration was 69 months. The results illustrated that the 5-year overall survival (OS) rates in the DCIS-MI and DCIS groups were 99.0% and 99.2%, respectively, and the 5-year disease-free survival (DFS) rates were 95.2% and 95.9%, respectively. Another study by Tianjin Cancer Hospital reached a similar conclusion.[23] However, these findings were based on studies with low numbers of patients and deaths. A retrospective clinical study based on the Surveillance, Epidemiology and End Results (SEER) database enrolled a total of 525,395 women diagnosed with either first primary DCIS or small ($\leq$2.0 cm) node-negative invasive breast cancer between 1990 and 2013.[24] According to the size of the invasive component of the primary tumor, 161,394 women had pure DCIS, 13,489 women had microinvasive carcinoma (invasive

Table 2. Comparison of outcomes between DCIS and DCIS-MI.[21]

Characteristic	DCIS N = 321	DCIS-MI N = 72	P
Age (years)			0.45
<50	113	22	
≥50	208	50	
ER			0.23
Positive	3	7	
Negative	7	5	
Unknown	311	60	
PR			>0.99
Positive	3	4	
Negative	6	5	
Unknown	312	63	
Hormonal therapy			0.069
Yes	66	8	
No	250	62	
Unknown	5	2	
Outcome			
10-year LRFS	89%	90.7%	0.36
10-year DMFS	98.5%	97.9%	0.77
10-year OS	93.2%	95.7%	0.93
Local relapse	22 (6.8%)	6 (8.3%)	0.36

DCIS, ductal carcinoma in situ; DCIS-MI, DCIS with microinvasion; ER, estrogen receptor; PR, progesterone receptor; LRFS, local relapse-free survival; DMFS, distant metastasis-free survival; OS, overall survival.

component size ≤0.1 cm), 153,856 women had invasive cancer (invasive component size = 0.2 to 1.0 cm), and 196,656 women had invasive cancer (invasive component size = 1.1 to 2.0 cm). As detailed in Table 3, the median follow-up period was 7.7 years, and 15,613 women died of breast cancer, including 1837 women with pure DCIS (1.1%), 323 women with DCIS-MI (2.4%), 3661 women with DCIS-IDC and an invasive component size of 0.2 to 1.0 cm (2.4%), and 9792 women with DCIS-IDC and an invasive component size of 1.1 to 2.0 cm (5.0%). At 20 years, the actuarial rate of breast cancer mortality was 3.8% for patients with pure DCIS, 6.9% for patients with DCIS-MI, 6.8% for patients with DCIS-IDC and an invasive component size of 0.2 to 1.0 cm, and 12.1% for women with DCIS-IDC and an invasive component size of 1.1 to 2.0 cm. The study demonstrated that the prognosis of patients with DCIS-MI was worse than that of patients with pure DCIS but identical to that of women with DCIS-IDC (6.8%).

Table 3. Comparison of outcomes in DCIS, DCIS-MI, T1a, and T1b.[24]

Characteristic	DCIS N = 161,394	DCIS-MI N = 13,489	T1a N = 153,856	T1b N = 196,656
Tumor grade				
I	17,752 (14.3%)	2058 (23.9%)	56,020 (39.8%)	42,991 (23.7%)
II	51,118 (41.2%)	3291 (38.2%)	60,911 (43.3%)	84,409 (46.5%)
III/IV	55,327 (44.5%)	3269 (37.9%)	23,769 (16.9%)	54,009 (29.8%)
Unknown	37,197	4871	13,156	15,247
Radiation				
No	88,601 (56.0%)	7439 (56.2%)	63,232 (41.9%)	90,384 (47.1%)
Yes	69,570 (44.0%)	5799 (43.8%)	87,513 (58.1%)	101,449 (52.9%)
Unknown	3223	251	3111	4823
Outcome				
BC death	1837 (3.8%)	323 (6.9%)	3661 (6.8%)	9792 (12.1%)

DCIS, ductal carcinoma in situ; DCIS-MI, DCIS with microinvasion; T1a, tumor diameter greater than 1 mm but less than 10 mm; T1b, tumor diameter greater than 10 mm but less than 20 mm; BC, breast cancer.

Treatments

Surgical operation

Local treatment of breast cancer. At present, the surgical methods for operable breast cancer include local tumor resection, conservative breast surgery, and total breast mastectomy. A large number of prospective studies have confirmed that local resection alone is not sufficient for the treatment of DCIS, and subsequent local radiotherapy can significantly reduce the local recurrence rate. Therefore, whether the prognosis of DCIS-MI is similar or worse than that of DCIS, combination of local resection and radiotherapy or chemotherapy is recommended.

Mamtani *et al.*[25] conducted a large retrospective study enrolling 121,080 patients with DCIS using the SEER database over the period of 1991 to 2010 and found that conservative breast surgery plus postoperative radiotherapy was superior to mastectomy in terms of the OS or DFS rate for DCIS. The data illustrated the proportion of patients undergoing breast-conserving surgery in the United States increased from 24.2% to 46.8%, whereas the percentage of patients undergoing mastectomy decreased from 44.9% to 19.3%. Among the patients, 43% received breast-conserving surgery and radiotherapy, 23.8% underwent mastectomy of the affected side, and the remaining patients underwent simple tumor resection or bilateral mastectomy. The median follow-up period was 71 months. The results demonstrated that the 5- and 10-year survival rates were 96.8% and 89.6%, respectively, in the breast-conserving surgery plus radiotherapy group, compared with 92.3% and 89.6%, respectively, in the and mastectomy group. The difference was statistically significant between the groups ($P < 0.05$). Similarly, the 10-year DFS rate was as high as 98.8% in the breast-conserving surgery group, versus 98.5% the in total mastectomy group.

Two other large retrospective analyses[26,27] confirmed that breast-conserving surgery plus postoperative radiotherapy was superior to single-breast resection for patients with early breast cancer. At the same time, it was suggested that age < 40 years, multiple foci or centers, vascular tumor thrombus, tumor location in the central area or inner quadrant, and high nuclear grade were high risk factors for the local recurrence of breast cancer.

At present, a large-scale retrospective analysis of DCIS-MI treatment is needed, although some small retrospective analysis revealed no difference in recurrence rates between breast-conserving surgery and mastectomy.[28] Because patients with DCIS-MI did not receive a significant benefit from mastectomy, conservative breast surgery should be considered preferentially. However, breast-conserving treatment for DCIS is appropriate in patients with a limited extent of disease. It is recommended to resect the breast when the tumor is multifocal or multicentric with a large mass, extensive malignant microcalcification, and taboo on radiotherapy.

Management of axillary lymph nodes. DCIS-MI is an uncommon clinical entity. Because of its rarity, its surgical axillary management remains controversial. The rate of axillary lymph node metastasis is approximately 0% to 20% in DCIS-MI.[29–36] It is crucial to distinguish between clinical node positivity and node negativity with positive sentinel lymph node biopsy (SLNB). SLNB is a standard examination for patients with breast cancer and clinically negative lymph nodes. For patients with positive SLNB, axillary lymph node dissection (ALND) is

the standard of care. Patients with negative SLNB do not require further surgical management of the axilla. However, in a recent study investigating the role of SLNB in DCIS-MI, Magnoni and colleagues[33] found that SLNB was not a good predictor of the need for ALND. Among 257 women with microinvasive breast cancer, 87.9% (266) had negative SLNB, and 12.1% (31) had positive SLNB. Among the 31 patients with positive SLNB, 5, 14, and 12 patients had macrometastases, micrometastases, and isolated tumor cells in sentinel nodes, respectively. Among them, 16 patients underwent ALND. After a median follow-up of 11 years, only 1 of 15 patients with positive SLNB who did not undergo ALND developed regional recurrence. The rate of regional recurrence did not differ according to the receipt of ALND. Fan et al.[37] confirmed that SLNB metastases are rare in patients with DCIS-MI. These findings suggest that SLNB may not be helpful in DCIS-MI owing to the low risk of lymph node metastasis and good prognosis, and fewer surgeries can achieve the same OS with better quality of life for patients.

Systemic treatment

The NSABP B-24 study[38] demonstrated that patients with ER-positive DCIS benefitted from adjuvant endocrine therapy. The NATO study[39] revealed that tamoxifen improved the 5-year tumor-free and total survival rates among patients with HR-positive invasive carcinoma compared with non-endocrine therapy. Thus, it is believed that patients with HR-positive DCIS-MI will benefit from adjuvant endocrine therapy.

Regarding adjuvant chemotherapy and targeted therapy, there is lack of evidence-based medical evidence. According to the guidelines, chemotherapy and targeted treatment are not recommended for patients with DCIS-MI without axillary lymph node involvement, whereas postoperative chemotherapy and targeted therapy are recommended while for patients with DCIS-MI and axillary lymph node metastasis.

Conclusions

DCIS-MI represents an intermediate state between DCIS and IDC. The final definition of DCIS with microinvasion is an invasive focus diameter of $\leq 1\,mm$ and a maximum focus diameter of less than 1 mm in patients with multiple invasive foci. The present literature is conflicting regarding the prognosis of DCIS-MI. Some studies concluded that the natural history of DCIS-MI is similar to that of pure DCIS, whereas the studies with the largest cohorts[24] suggested that DCIS-MI has a worse prognosis than pure DCIS and a comparable prognosis as DCIS-IDC. The reason for the two conclusions is that the former studies included small numbers of cases and deaths and used different definitions of microinvasion. In the management of DCIS-MI, factors such as nodal involvement, the Ki-67 status, and hormone receptor expression should be considered. Patients with DCIS-MI should receive nodal staging, and adjuvant chemotherapy or irradiation should be administered to those with node-positive disease. Current studies suggested that the prognosis of patients receiving additional radiotherapy after conservative breast surgery is better than that of patients receiving conservative breast surgery alone. Management of the axilla in breast cancer remains a controversial topic. Recent studies indicated SLNB may not be useful in patients with DCIS-MI because of its low risk of lymph node metastasis and good prognosis.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

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