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ORIGINAL RESEARCH

Risk factors for lymph node metastasis and the impact of adjuvant chemotherapy on ductal carcinoma in situ with microinvasion: a population-based study

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Background: Ductal carcinoma in situ with microinvasion (DCISM) represents ~1% of all breast cancer cases. Risk factors for lymph node (LN) metastasis and appropriate adjuvant therapy for DCISM are still widely debated.

Methods: We retrieved DCISM data from the National Cancer Institute's Surveillance, Epidemiology, and End Results registry database (1998–2013). Chi-squared tests and logistic regression models were applied to investigate the potential risks of LN metastasis. Univariate and multivariate Cox proportional hazards regressions were performed to estimate the prognostic factors of DCISM. Survival outcomes were estimated using the Kaplan–Meier method. A 1:1 propensity score matching was used to minimize potential bias.

Results: Overall, 6,219 patients with DCISM met our inclusion criteria. Younger age and higher grade disease were identified as risk factors for LN metastasis. In the multivariable analysis, LN metastasis and chemotherapy were prognostic factors for worse overall survival and breast cancer-specific survival. Furthermore, propensity score matching and subgroup analysis showed that chemotherapy may not be effective for DCISM patients.

Conclusion: Younger patients with high-grade disease tend to have LN involved in DCISM. Adjuvant chemotherapy might not be necessary for patients with DCISM.

Keywords: SEER database, breast cancer, ductal carcinoma in situ with microinvasion, adjuvant chemotherapy, lymphatic metastasis

Introduction

Ductal carcinoma in situ with microinvasion (DCISM) is a rare pathologic entity accounting for ~0.6%–3.4% of all breast cancer cases.[1,2] The specific definitions of this entity have varied in the past decades, and the seventh edition of the American Joint Committee on Cancer *Cancer Staging Manual* defines microinvasion as not exceeding 1 mm in size.[3] With the widespread use of mammography in screening, increasing numbers of DCISM are now being detected and diagnosed.

The presence of lymph node (LN) metastasis has been reported to range between 0% and 25%.[4–9] Although many pathological factors might be associated with LN metastasis, including lymph angiogenesis,[7] high-grade disease,[10] larger ductal carcinoma in situ (DCIS) lesion,[11] and younger age,[9] the reliability of these conclusions should be interpreted carefully due to the small number of studies.

DCISM presents a therapeutic conundrum. The prognosis falls somewhere between invasive cancer and DCIS, but the specific prognosis of individuals is

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unclear, and risk stratification based on retrospective reports has been difficult due to the overall rarity of this entity.[12] Although classified as invasive cancer, DCISM has an excellent prognosis compared with DCIS.[4] Unfortunately, an agreement has not been reached on the standard therapy for DCISM. Adjuvant chemotherapy is generally recommended for invasive ductal carcinoma (IDC) with LN metastasis, while it remains undetermined whether DCISM with LN involvement should receive chemotherapy.

Based on retrieved DCISM data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry database (1998–2013), we designed a population-based study to identify risk factors for LN metastasis in DCISM and, more importantly, weigh the impact of adjuvant chemotherapy on DCISM.

Methods

Patient selection

Data were extracted from the National Cancer Institute's SEER program between 1998 and 2013. The SEER project is a United States population-based cancer registry that began in 1973 and now includes 18 registries across the United States, covering ~28% of the American population.

We focused on cases diagnosed between 1998 and 2013 with microscopically confirmed stage T1mic, and we selected patients aged between 20 and 70 years old. Information about patients with infiltrating duct carcinoma (code 8500/3) was referenced to the International Classification of Diseases for Oncology, version 3. Patients who were identified at autopsy, with death certificate only, no surgery treatment, or incomplete survival times were excluded from our study. Tumor demographics included grade (grade I: well differentiated/grade II: moderately differentiated/grade III: poorly differentiated/grade IV: undifferentiated/unknown), hormone status (estrogen receptor [ER] positive/negative/unknown, progesterone receptor [PR] positive/negative/unknown), and human epidermal growth factor receptor 2 (HER2) status (positive/negative/unknown). Treatment characteristics included surgery (lumpectomy/mastectomy), chemotherapy, and radiotherapy. Additionally, as SEER did not report the type of LN surgery, we used the number of LNs excised as an alternative. We define patients with 1–5 LNs removed as sentinel lymph node biopsy (SLNB) and >5 LNs removed as axillary lymph node dissection (ALND), as previous studies reported.[13,14] A total of 6,219 female patients with DCISM met our inclusion criteria.

Statistical analysis

The characteristics of the two groups of patients (LN positive vs LN negative) were compared using Pearson's chi-squared test or Fisher's exact test. Logistic regression analysis was further used to identify the independent factors associated with LN metastasis. Overall survival (OS) was calculated as the time from the date of diagnosis to the date of death from any cause. Breast cancer-specific survival (BCSS) was measured from the date of diagnosis to the date of death owing to breast cancer. Survival rates were assessed using the Kaplan–Meier method and compared using the log-rank test. Furthermore, we used the Cox proportional hazards model to calculate HR and 95% CI for the prognostic factors of DCISM. To minimize group differences, a 1:1 propensity score matching was used.

All statistical analyses were performed using SPSS statistical software, version 22.0 (IBM Corporation, Armonk, NY, USA), and a P-value <0.05 was considered statistically significant.

Ethics statement

This was a retrospective analysis using data from the SEER database, which is a public health database. The data released by the SEER database were publicly accessible to applicants and did not require informed patient consent for use.

Results

Patient and treatment characteristics

The characteristics of all patients are listed in Table S1. The mean (range) age at diagnosis of DCISM was 53.8 (20–70) years. Overall, the majority (74.5%) of patients were white. More than half (58.4%) of the patients had low-grade disease (grade I+II). Moreover, 68.7% of patients had positive ER expression, and 55.2% had positive PR expression. Only 7.8% of patients had LN metastasis. As SEER began recording HER2 status in 2010, there was little information available for this subgroup.

For surgical treatment, SLNB was performed in 4,102 patients (66.4%), lumpectomy was performed in 3,388 patients (54.5%), corresponding to 1,496 patients (24.2%) with ALND and 2,831 patients (45.5%) with mastectomy. In addition, 46.9% of patients underwent radiotherapy, and a small number of patients (9.8%) received chemotherapy.

LN positive vs LN negative

We then divided DCISM into two groups: LN positive and LN negative. There was no difference in ER (P=0.396), PR (P=0.414), and HER2 (P=0.126) expression, but much

more high-grade diseases and young patients were observed in the LN-positive group (50.9% vs 41.5%, $P<0.001$; 30.1% vs 17.4%, $P<0.001$, respectively). Age at diagnosis, ethnicity, grade, hormone receptor status, and HER2 status were analyzed in the binary logistic regression model. Using the multivariate analysis, younger age and higher grade disease were found to be independent risk factors responsible for LN metastasis. The results of the univariate and multivariate analyses are summarized in Tables 1 and 2.

Survival outcomes

The median follow-up was 76 months (range, 1–170 months). There were 271 deaths in all and 90 breast cancer-specific deaths. The 10-year OS and BCSS of all patients were 93.8% and 97.7%, respectively. The 10-year OS for LN-negative patients was 94.7%, compared to 87.4% in the LN-positive group (Figure 1A; $P<0.001$), and the 10-year BCSS for LN-negative patients was 98.4%, compared to 91.3% in the LN-positive group (Figure 1B; $P<0.001$).

Table 1 Patient characteristics stratified by lymph node status and univariate analysis of risk factors of lymph nodes metastasis

Variables	LN positive	%	LN negative	%	*P*-value
Age (years)					<0.001
<45	131	30.1	905	17.4	
≥45	304	69.9	4,288	82.6	
Ethnicity					<0.001
White	320	73.6	3,863	74.4	
Black	77	17.7	592	11.4	
Other	38	8.7	738	14.2	
Grade					0.001
I+II	158	49.1	2,045	58.5	
III+IV	164	50.9	1,448	41.5	
Unknown	113		1,700		
ER status					0.396
Negative	132	33.8	1,411	31.7	
Positive	259	66.2	3,044	68.3	
Unknown	44		738		
PR status					0.414
Negative	181	47.3	1,948	45.1	
Positive	202	52.7	2,372	54.9	
Unknown	52		873		
HER2 status					0.126
Negative	54	52.9	693	60.7	
Positive	48	47.1	449	39.3	
Unknown	333		4,051		
Radiotherapy					<0.001
No	282	65.1	2,750	53.2	
Yes	151	34.9	2,420	46.8	
Unknown	2		23		
Chemotherapy					<0.001
No	130	29.9	4,921	94.8	
Yes	305	70.1	272	5.2	
LN surgery					<0.001
SLNB	121	27.9	3,981	77.1	
ALND	313	72.1	1,182	22.9	
Unknown	1		30		
Breast surgery					<0.001
Lumpectomy	112	25.7	2,813	54.2	
Mastectomy	323	74.3	2,380	45.8	
Vital status					<0.001
Alive	386	88.7	5,010	96.5	
Dead of other cause	19	4.4	135	2.6	
Breast cancer-specific death	30	6.9	48	0.9	

Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LN, lymph node; PR, progesterone receptor; SLNB, sentinel lymph node biopsy.

Table 2 Multivariable regression analysis evaluating factors associated with lymph nodes metastasis

Variables	HR (95% CI)	*P*-value
Age (years)		<0.001
<45	Reference	
≥45	0.496 (0.398–0.617)	
Ethnicity		0.001
White	Reference	
Black	1.547 (1.186–2.018)	
Grade		0.008
I+II	Reference	
III+IV	1.385 (1.088–1.763)	

Prognostic factor

In the univariate analysis, age at diagnosis, ethnicity, tumor grade, PR status, LN status, radiotherapy, chemotherapy, and surgery treatment were significantly associated with OS or (and) BCSS.

In the multivariate analysis, older age (HR 1.762, 95% CI 1.228–2.529, *P*=0.002), black women (HR 2.188, 95% CI 1.645–2.910, *P*<0.001), LN metastasis (N2: HR 3.697, 95% CI 1.818–7.519, *P*<0.001; N3: HR 6.846, 95% CI 1.989–23.568, *P*=0.002), and chemotherapy (HR 1.701, 95% CI 1.133–2.555, *P*=0.010) were associated with worse OS. However, positive PR expression (HR 0.559, 95% CI 0.385–0.811, *P*=0.002) and radiotherapy (HR 0.597, 95% CI 0.426–0.837, *P*=0.003) were significantly good predictors of breast cancer OS. Moreover, black women (HR 2.081, 95% CI 1.243–3.484, *P*=0.005), LN metastasis (N2: HR 4.732, 95% CI 1.977–11.324, *P*<0.001; N3: HR 7.139, 95% CI 1.449–35.161, *P*=0.016), chemotherapy (HR 3.938, 95% CI 2.168–7.153, *P*<0.001), and mastectomy (HR 2.163, 95% CI 1.182–3.956, *P*=0.012) were related with worse BCSS. As the majority of HER2 variables was not known (SEER database collected HER2 information after 2010), the results

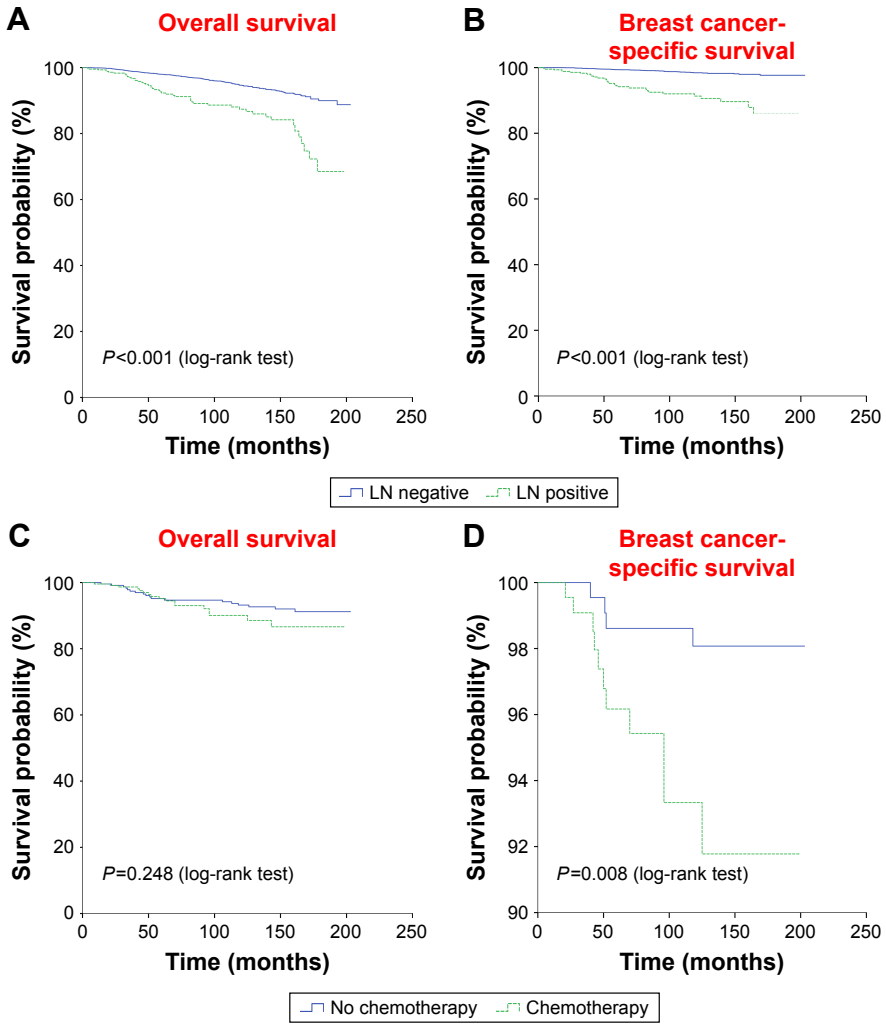

Figure 1 DCISM survival outcomes estimated by the Kaplan–Meier method.
Notes: Breast cancer overall survival curves (**A**) and breast cancer-specific survival curves (**B**) for patients with DCISM, stratified by LN status. Breast cancer overall survival (**C**) and breast cancer-specific survival (**D**) stratified by chemotherapy after propensity score matching.
Abbreviations: DCISM, ductal carcinoma in situ with microinvasion; LN, lymph node.

of HRs were insignificant in the univariate and multivariate analyses. The results of univariate and multivariate analyses are listed in Table 3.

Propensity score matching

Patients who received chemotherapy may have been subject to some selection bias. To further adjust for potential baseline bias and confounders, propensity score matching was carried out. Moreover, to minimize confounders, we also excluded some unavailable or unknown information, such as unknown ER status, PR status, LN stage, and radiotherapy. Finally, a total of 3,198 patients with complete information were available. All matching variables were balanced between the two groups (chemotherapy vs no chemotherapy); details of the original, unmatched cohort, and propensity-matched cohort are shown in Table 4. After matching, survival analysis and log-rank testing revealed worse BCSS in the chemotherapy-treated group than in the no chemotherapy group (Figure 1D; P=0.008), but there was no statistical significance for OS (Figure 1C; P=0.248).

In the LN-negative subgroup, the same methods were implemented as earlier. Finally, 2,916 LN-negative patients with complete information were available; details of the original, unmatched cohort, and propensity-matched cohort are shown in Table S2. After matching, survival analysis showed no statistical significance in the two groups (chemotherapy vs no chemotherapy) for OS (Figure S1A; P=0.324) and BCSS (Figure S1B; P=0.121). Unfortunately, due to the limited number, we could not apply propensity score matching to the LN-positive subgroup.

Subgroup analysis

Univariate and multivariate Cox proportional hazards regression models were also employed in the LN-negative and LN-positive subgroups. For the LN-negative subgroup, chemotherapy was an independent factor for worse OS (HR 2.119, 95% CI 1.311–3.424, P=0.002) and BCSS (HR 4.631, 95% CI 2.253–9.114, P<0.001), as shown in Table S3. For the LN-positive subgroup, chemotherapy was not associated with better OS (P=0.559) and BCSS (P=0.288), as shown in Table S4.

Discussion

DCISM is a disease entity that is not fully characterized, in contrast to DCIS and IDC. The clinical-pathological characteristics are unclear, and the optimal treatment is controversial due to limited information. Although there have already been two studies about DCISM based on the SEER database,[15,16] they focused on comparing DCISM with

Table 3 Univariate and multivariate Cox regression analyses for overall and breast cancer-specific survival

Variables	Overall survival				Breast cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)								
<45	Reference		Reference		Reference		Reference	
≥45	1.555 (1.090–2.218)	0.015	1.762 (1.228–2.529)	0.002	0.534 (0.340–0.838)	0.006	0.763 (0.480–1.215)	0.255
Ethnicity								
White	Reference		Reference		Reference		Reference	
Black	2.295 (1.731–3.042)	<0.001	2.188 (1.645–2.910)	<0.001	2.333 (1.346–3.704)	0.006	2.081 (1.243–3.484)	0.005
Others	0.473 (0.288–0.777)	0.003	0.474 (0.288–0.780)	0.003	0.892 (0.457–1.743)	0.738	0.911 (0.463–1.793)	0.788
Grade								
I+II	Reference		Reference		Reference		Reference	
III+IV	0.993 (0.742–1.328)	0.960	0.891 (0.657–1.208)	0.456	2.053 (1.226–3.438)	0.006	1.533 (0.892–2.632)	0.122
Unknown	1.065 (0.800–1.419)	0.666	1.042 (0.779–1.395)	0.780	1.461 (0.842–2.537)	0.178	1.369 (0.781–2.401)	0.273
ER								
Negative	Reference		Reference		Reference		Reference	
Positive	0.851 (0.634–1.143)	0.284	1.314 (0.899–1.921)	0.159	0.666 (0.411–1.080)	0.099	1.386 (0.731–2.627)	0.317
Unknown	1.118 (0.810–1.542)	0.499	1.141 (0.562–2.315)	0.716	0.814 (0.468–1.415)	0.466	0.786 (0.254–2.439)	0.677

(Continued)

Table 3 (*Continued*)

Variables	Overall survival				Breast cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
PR								
Negative	Reference		Reference		Reference		Reference	
Positive	0.646 (0.482–0.867)	0.004	0.559 (0.385–0.811)	0.002	0.516 (0.311–0.859)	0.011	0.525 (0.272–1.013)	0.055
Unknown	1.005 (0.753–1.341)	0.972	0.966 (0.501–1.863)	0.917	0.839 (0.510–1.380)	0.490	1.602 (0.574–4.472)	0.368
HER2 status								
Negative	Reference		Reference		Reference		Reference	
Positive	0.661 (0.171–2.557)	0.549	0.470 (0.119–1.851)	0.280	<0.001 (0–999)	0.953	<0.001 (0–999)	0.952
Unknown	1.296 (0.599–2.801)	0.510	1.119 (0.512–2.443)	0.779	1.596 (0.382–6.673)	0.522	1.224 (0.279–5.373)	0.789
LN status								
N0	Reference		Reference		Reference		Reference	
N1	2.406 (1.676–3.455)	<0.001	1.463 (0.926–2.311)	0.103	5.059 (2.973–8.609)	<0.001	1.480 (0.755–2.903)	0.254
N2	5.383 (2.929–9.892)	<0.001	3.697 (1.818–7.519)	<0.001	16.798 (8.242–34.237)	<0.001	4.732 (1.977–11.324)	<0.001
N3	8.295 (2.649–25.977)	<0.001	6.846 (1.989–23.568)	0.002	20.990 (5.097–86.436)	<0.001	7.139 (1.449–35.161)	0.016
Unknown	1.548 (1.095–2.188)	0.013	0.821 (0.092–7.310)	0.860	1.874 (0.995–3.531)	0.052	1.001 (0.067–14.902)	0.999
Radiotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.585 (0.453–0.754)	<0.001	0.597 (0.426–0.837)	0.003	0.440 (0.275–0.702)	0.001	0.625 (0.346–1.129)	0.119
Unknown	1.119 (0.278–4.510)	0.874	0.832 (0.203–3.402)	0.798	1.539 (0.213–11.094)	0.669	0.750 (0.097–5.791)	0.782
Chemotherapy								
No	Reference		Reference		Reference		Reference	
Yes	2.332 (1.744–3.118)	<0.001	1.701 (1.133–2.555)	0.010	6.933 (4.574–10.508)	<0.001	3.938 (2.168–7.153)	<0.001
LN surgery								
No	Reference		Reference		Reference		Reference	
SLNB	0.585 (0.404–0.848)	0.005	0.475 (0.051–4.392)	0.511	0.476 (0.237–0.959)	0.038	0.347 (0.021–5.749)	0.460
ALND	1.004 (0.697–1.448)	0.981	0.549 (0.059–5.092)	0.598	1.479 (0.769–2.844)	0.241	0.455 (0.027–7.589)	0.584
Unknown	1.291 (0.461–3.618)	0.627	1.043 (0.137–7.912)	0.968	2.235 (0.495–10.084)	0.296	1.528 (0.171–13.635)	0.704
Breast surgery								
Lumpectomy	Reference		Reference		Reference		Reference	
Mastectomy	1.610 (1.265–2.050)	<0.001	1.140 (0.818–1.590)	0.439	3.600 (2.226–5.822)	<0.001	2.163 (1.182–3.956)	0.012

Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LN, lymph node; PR, progesterone receptor; SLNB, sentinel lymph node biopsy.

Table 4 Baseline characteristics of DCISM patients treated with or without chemotherapy

Variables	Original, unmatched cohort				*P*-value	Propensity-matched cohort				*P*-value
	No chemotherapy		Chemotherapy			No chemotherapy		Chemotherapy		
	No	%	No	%		No	%	No	%	
Age (years)					<0.001					0.450
<45	470	16.8	120	30.3		53	22.6	60	25.5	
≥45	2,332	83.2	276	69.7		182	77.4	175	74.5	
Ethnicity					0.469					0.849
White	2,092	74.7	291	73.5		174	74.0	177	75.3	
Black	331	11.8	55	13.9		30	12.8	26	11.1	
Other	379	13.5	50	12.6		31	13.2	32	13.6	
Grade					<0.001					0.517
I+II	1,692	60.4	169	42.7		110	46.8	103	43.8	
III+IV	1,110	39.6	227	57.3		125	53.2	132	56.2	
ER status					<0.001					0.782
Negative	799	28.5	184	46.5		110	46.8	113	48.1	
Positive	2,003	71.5	212	53.5		125	53.2	122	51.9	
PR status					<0.001					0.396
Negative	1,188	42.4	231	58.3		137	58.3	146	62.1	
Positive	1,614	57.6	165	41.7		98	41.7	89	37.9	
LN status					<0.001					0.797
N0	2,728	97.4	188	47.5		183	77.9	183	77.9	
N1	70	2.5	165	41.7		48	20.4	45	19.1	
N2	4	0.1	35	8.8		4	1.7	6	2.6	
N3	0	0	8	2.0		0	0	1	0.4	
Radiotherapy					0.035					0.778
No	1,448	51.7	227	57.3		137	58.3	140	59.6	
Yes	1,354	48.3	169	42.7		98	41.7	95	40.4	
LN surgery					<0.001					0.115
SLNB	2,201	78.6	161	40.7		122	51.9	139	59.1	
ALND	601	21.4	235	59.3		113	48.1	96	40.9	
Breast surgery					<0.001					0.578
Lumpectomy	1,555	55.5	139	35.1		108	46.0	102	43.4	
Mastectomy	1,247	44.5	257	64.9		127	54.0	133	56.6	

Abbreviations: ALND, axillary lymph node dissection; DCISM, ductal carcinoma in situ with microinvasion; ER, estrogen receptor; LN, lymph node; PR, progesterone receptor; SLNB, sentinel lymph node biopsy.

DCIS and IDC and did not analyze the therapy strategies, such as chemotherapy and surgical options. We first divided the DCISM into two groups (LN positive vs LN negative) to explore the difference between the two groups and identify the potential risks for LN metastasis. To our knowledge, this population-based study is the first to identify predictive markers for LN metastasis and report the potential influence of adjuvant chemotherapy on DCISM.

There is a potential risk of LN metastasis in DCISM. Some studies reported that it was valuable to perform SLNB routinely,[9] while others had different perspectives and stated that SLNB should be individualized.[17] These debates raised the question of whether there were subgroups of patients who were at high risk of LN metastasis.

In our study, 7.8% of patients had LN metastasis. Importantly, our study identified that younger age and higher grade disease were risk factors for LN involvement. In a study of 81 patients with DCISM, Gray et al suggested that extensive size of DCIS (>5 cm) and multifocal microinvasion were associated with LN metastasis.[5] Wasserberg et al revealed that nuclear grade, comedonecrosis, and DCIS-involved ducts might predict LN metastasis. However, only high-grade status was a significant factor for LN metastasis in T1a breast cancer.[10] Kapoor et al analyzed 45 patients with DCISM and found that the LN was involved in nine patients. In the multivariate analysis, only negative ER status ($P<0.02$) was a risk factor for LN metastasis rather than high-grade disease, comedonecrosis, lymphovascular invasion, DCIS size, multifocal microinvasion, and HER2 status.[18] However, several studies have proposed contrary conclusions. Guth et al proposed that comedonecrosis, nuclear grade, multifocal DCIS, and hormone receptor status might not predict LN involvement, but patients with LN positivity tended to be younger,[9] which is consistent with our current study. Pimiento et al studied the correlation between clinical-pathological features and axillary LN metastasis in 90 female patients

with DCISM. Unfortunately, this study failed to identify any significant predictive factor.[19] In addition, by studying records from a prospective institutional database, Matsen et al investigated 414 patients with DCISM and suggested that multifocal microinvasion may not be correlated with LN involvement.[12] All these published studies were limited by small sample size, and the reliability of their conclusions is therefore not confirmed. Larger studies are urgently needed to identify the relevant predictive factors of LN metastasis in patients with DCISM.

To take it further, the significance of LN involvement in DCISM is another topic of interest – specifically, the predictive value of LN involvement on locoregional recurrence and distant metastasis. Unfortunately, the SEER database cannot provide this critical information.

The other interesting finding from our current study is that adjuvant chemotherapy might not be necessary for DCISM. Especially for the subgroup of LN-negative patients, chemotherapy is even a risk prognostic factor for worse OS (HR 2.119, 95% CI 1.311–3.424, P=0.002) and BCSS (HR 4.631, 95% CI 2.253–9.114, $P<0.001$). Although, we could not apply propensity score matching to investigate the effect of chemotherapy in the LN-positive subgroup (it may be underpowered to do so), univariate and multivariate Cox proportional hazards regression models suggested that chemotherapy was not associated with better OS (P=0.559) and BCSS (P=0.288).

Because chemotherapy is seldom needed for DCISM, the impact of chemotherapy on this uncommon entity is unclear until now. Fang et al presented 84 DCISM patients, 16 of whom were treated with chemotherapy and trastuzumab. After univariate and multivariate analyses, HER2 status was an independent predictor for worse disease-free survival with a median follow-up of 31 months, and they suggested that chemotherapy and target therapy in patients with HER2-positive disease seemed to be reasonable.[20] Matsen et al reported that patients with LN involvement and multifocal microinvasion were more likely to receive chemotherapy.[12] Lyons et al found 14 patients with positive sentinel LN (SLN) among 112 patients with DCISM, and adjuvant chemotherapy was given to all patients with macrometastasis. With a median follow-up of 6 years, there were five local recurrences. It is worth discussing that all five recurrences were observed in patients with negative SLNs. Thus, the authors concluded that DCISM patients with SLN macrometastasis would benefit from adjuvant chemotherapy.[21] On the other hand, regardless of LN metastasis, DCISM patients also reported excellent prognosis.[22,23] Therefore, adjuvant therapy may be unnecessary for this already excellent prognosis disease.[24] Niu et al found no statistical significance in the 5-year disease-free survival or OS between chemotherapy and non-chemotherapy groups but it might improve the outcomes of ER-negative/PR-negative DCISM patients.[25] According to the latest guidelines, including National Comprehensive Cancer Network guidelines, chemotherapy was routinely recommended for breast cancer patients with LN involvement.[26] However, it is unclear whether patients were potentially overtreated or the relatively rare recurrence in the node-positive group was due to adjuvant chemotherapy.[27] The MINDACT trial is a phase III trial comparing the 70-gene signature with the commonly used clinicopathologic criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0–3 positive nodes. It is worth noting that early results from the MINDACT trial suggest that the 70-gene signature can help avoid chemotherapy in certain patients regardless of larger tumor size and nodal status, without compromising the outcome.[28] Based on these data, in the era of precision medicine, clinicians should consider the biology of tumors while making clinical decisions. The costs and benefits of chemotherapy should be exactly weighted in DCISM patients. In addition, patients who can derive the most benefit from chemotherapy should be further identified.

Our present study has several limitations. First, when both in situ and invasive components are present in a tumor, the SEER database records only the characteristics of the invasive component; therefore, we cannot analyze the impacts of DCIS lesions on LN metastasis. In addition, potentially significant clinicopathological factors, such as vascular invasion, surgical margin status, adjuvant endocrine therapy, and targeted therapy, are not provided by the SEER database. Besides, HER2 status was not available before 2010 in the SEER database. The number of analyzed patients was very limited when HER2 status is considered, specifically in the propensity score matching analysis. Furthermore, due to the retrospective design of our study, there may be some inherent biases. Finally, agreement on chemotherapy between the SEER database and chart reviews proved to be moderate.[29] The preferred approach would be to combine data from different sources to obtain more complete information.

Conclusion

Younger patients with high-grade disease tend to have LN metastasis in DCISM. DCISM patients are unlikely to benefit from adjuvant chemotherapy. Further studies and randomized trials should be performed before any appropriate suggestion can be made.

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Author contributions

Zhou J and Wang L designed the study; Zhou J and Chen C wrote the manuscript; Chen C, Huang S, Huang A, Jia Y, Wang J, and Mao M analyzed the data and interpreted the results. All authors approved the final version to be published. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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