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Role of Primary Tumor Characteristics in Predicting Positive Sentinel Lymph Nodes in Patients with Ductal Carcinoma in situ or Microinvasive Breast Cancer

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Abstract

BACKGROUND—We determined the incidence of a positive sentinel lymph node (SLN) in patients with ductal carcinoma in situ (DCIS) or microinvasive breast cancer (MIC) and the predictive factors of SLN metastasis in these patients.

METHODS—We retrospectively identified which of 4,503 patients who had undergone SLN dissection (SLND) from March 1994 through March 2006 at our institution had a preoperative diagnosis or final diagnosis of DCIS or MIC. Clinicopathologic factors were examined by logistic regression analysis.

RESULTS—Of the 624 patients with a preoperative diagnosis of DCIS or MIC, 40 had a positive SLN (6.4%). Of the 475 patients with a final diagnosis of DCIS or MIC, 9 had a positive SLN (1.9%). Clinical DCIS size >5 cm was the only independent predictor of positive SLNs for both patients with a preoperative diagnosis and patients with a final diagnosis of DCIS or MIC. Core biopsy as the method of preoperative diagnosis and DCIS size >5 cm were independent predictors for a final diagnosis of invasive carcinoma in the 149 patients who had a preoperative diagnosis of DCIS or MIC.

CONCLUSIONS—SLND for patients with a diagnosis of DCIS should be limited to patients who are planned for mastectomy or who have DCIS size >5 cm. Patients who have a core needle biopsy diagnosis of DCIS have a higher risk of harboring invasive breast cancer on final pathologic assessment of the primary tumor. This information can be used in preoperative counseling of patients with DCIS regarding the timing of SLN biopsy.

Keywords

Ductal carcinoma in situ; Microinvasive breast cancer; Sentinel lymph node dissection; Metastasis

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Introduction

With the increasing use of screening mammography, the proportion of breast cancer diagnoses that are ductal carcinoma in situ (DCIS) has increased significantly. Today, DCIS accounts for 25% to 30% of breast cancers detected in population-screening programs[1]. In contrast, microinvasive breast cancer (MIC) is an uncommon pathologic entity that represents <1% of breast cancers[2]. Although lymph node involvement is identified in 1% to 2% of women with DCIS and <5% of women with MIC by traditional axillary lymph node dissection, the routine use of axillary lymph node dissection in these patients is not recommended[3]. Some physicians use instead sentinel lymph node dissection (SLND) in the evaluation of patients with DCIS or MIC because SLND limits the extent of axillary surgery by removing fewer nodes and because morbidity can be reduced compared with complete axillary lymph node dissection. The rate of SLN positivity in patients with pure DCIS is modest (approximately 2% to 13%)[4–7]. The routine use of SLND is debated because the rate of SLN positivity has been <3% in some studies[5, 7]. Many clinicians believe that certain subsets of patients are at high risk for microinvasive disease and subsequent axillary metastasis and may benefit more than other patients from the use of SLND[4, 8]. In addition, many surgeons will recommend SLND for patients with DCIS who undergo mastectomy because there will be no opportunity to perform lymphatic mapping after mastectomy if invasive disease is identified in the breast on final pathology review.

Whether SLND should be performed routinely for all patients with a preoperative diagnosis of DCIS or MIC or for only certain subsets of patients has been debated. The purpose of this study was to examine the results of SLND in a population of patients with DCIS or MIC to determine the incidence of SLN positivity and the factors predictive of SLN metastasis.

Patients and Methods

We used the surgical oncology breast cancer database to retrospectively evaluate 4,503 consecutive patients who had undergone SLND from March 1994 through March 2006 at our institution. Patients had undergone SLND, at the discretion of the treating surgeon, using filtered ^{99m}Tc-labeled sulfur colloid alone, 1% isosulfan blue dye alone, or a combination of the 2 agents. A node was judged to be a SLN if it had counts at least 5 times those of background radioactivity in vivo, was stained blue, or both. A positive SLN was defined as any tumor deposit >0.2 mm on frozen-section, standard hematoxylin and eosin staining, or immunohistochemical analysis.

Of the patients who had undergone SLND, we identified those who had a preoperative diagnosis of DCIS or MIC by core needle biopsy or excisional biopsy. We also determined which of those identified patients had the same final diagnosis, or a final diagnosis of invasive cancer, by pathologic assessment. MIC was defined as invasion ≤0.1 cm in the greatest dimension. The histologic grade of the primary tumors was determined according to the modified Black's nuclear grading system (grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated).[9]

Our study was approved by the M. D. Anderson Cancer Center Institutional Review Board. Patients who had been treated with neoadjuvant chemotherapy and those who had no identifiable SLNs at surgery were excluded from the study. The clinical factors examined were age at diagnosis, race, tumor location, presence of a palpable tumor, DCIS size (by clinical exam or imaging), and method of preoperative diagnosis. Pathologic factors evaluated were final histologic type, necrosis, type of DCIS, estrogen receptor status, progesterone receptor status, and histologic grade.

For statistical analysis, patients who had a preoperative diagnosis of DCIS or MIC were separated into SLN-positive and SLN-negative groups. Each clinicopathologic factor was compared between these 2 groups. Data were subjected to univariate analysis and then multivariate analysis. Stepwise multiple logistic regression analysis was used to identify variables that predicted for a positive SLN. This analysis was repeated for patients who had a final diagnosis of DCIS or MIC and again for patients who had a final diagnosis of invasive cancer. All *P* values were 2 tailed, and a value of ≤.05 was considered significant. Microsoft Access database software and Stata statistical software (StataCorp LP, College Station, TX) were used for compilation of the data and statistical analyses, respectively.

Results

Clinicopathologic predictors of a positive SLN with an initial diagnosis of DCIS or MIC

Of the 4,503 patients who had undergone SLND, 624 had a preoperative diagnosis of DCIS or MIC by biopsy. SLN metastases were detected in 40 (6.4%) of the 624 patients. In half of them, the SLN harbored only micrometastases (≤2 mm), whereas larger metastases were identified in the other half. The SLN was the only involved axillary lymph node in 37 (92.5%) patients. In univariate analysis, SLN metastasis was significantly associated with patient age, DCIS size, method of preoperative diagnosis, and final histologic type (Table 1). The multivariate analysis, with all the variables significant in the univariate analysis fitted simultaneously, documented an independent direct association of SLN metastasis with DCIS size 2 to 5 cm, DCIS size >5 cm, and final histologic type of invasive cancer (Table 2).

Clinicopathologic predictors of a positive SLN with a final diagnosis of DCIS or MIC

Of the 4,503 patients who had undergone SLND, 475 had a final diagnosis of DCIS or MIC by pathologic assessment. SLN metastases were detected in 9 (1.9%) of the 475 patients. In 8 patients, the SLN harbored only micrometastases (≤ 2 mm), whereas larger metastases were identified in 1 patient. The SLN was the only involved axillary lymph node in all 9 (100%) patients. In univariate analysis, SLN metastasis was significantly associated with only DCIS size (Table 3), and multivariate analysis revealed that DCIS size >5 cm was the only independent predictor of a positive SLN (Table 4).

Clinicopathologic predictors of invasive breast cancer

Of the 624 patients with a preoperative diagnosis of DCIS or MIC, 149 (23.9%) had a final diagnosis of invasive cancer on pathologic assessment. Of those 149 patients, core biopsy had been used to make the preoperative diagnoses for 129 (86.6%) and excisional biopsy had been used to make the preoperative diagnosis for 20 (13.4%). In univariate analysis,

invasive breast cancer was significantly associated with DCIS size, method used for the preoperative diagnosis, and necrosis (Table 5). Multivariate analysis revealed 2 independent predictors for a final diagnosis of invasive carcinoma: DCIS size >5 cm and core biopsy as the method of preoperative diagnosis.

Comments

SLND has been proposed for the surgical management of DCIS or MIC because it reveals nodal involvement in 2% to 13% of patients with breast cancer[4, 7]. Our results are consistent with those previously reported. In the current study, approximately 6% of patients with a preoperative diagnosis of DCIS or MIC had positive SLNs. Similar to the report by Kelly and colleagues[3], in our study, the incidence of positive SLNs in patients with a final diagnosis of DCIS or MIC was very low (1.9%).

In our study, multivariate analysis revealed 3 predictors of positive SLNs in patients with a preoperative diagnosis of DCIS or MIC: DCIS size 2 to 5 cm, DCIS size >5 cm, and final histologic diagnosis of invasive cancer. Data from other investigations have indicated that there is a direct relationship between the size of the primary tumor and the likelihood of axillary node metastases for cancers up to 5 cm in size and that tumor size is the most important factor that may contribute to the likelihood of a positive SLN[10]. Our findings are consistent with this notion. Not surprisingly, invasive cancer was another predictor of positive SLNs. Our further analysis revealed that DCIS size and final histologic type of invasive cancer were associated with each other. Patient age and method of preoperative diagnosis may serve as additional predictors, both being significant on univariate analysis but not on multivariate analysis in our study. It is likely that younger age and invasive histology are also associated with each other. DCIS size >5 cm was also the only predictor of positive SLNs on multivariate analysis in patients with a final diagnosis of DCIS or MIC.

Because final histologic type as invasive cancer was an important predictor of positive SLNs, we also looked at the clinicopathologic predictors of invasive cancer in patients with a preoperative diagnosis of DCIS or MIC. Multivariate analysis revealed 2 independent predictors of invasive cancer in patients with a preoperative diagnosis of DCIS or MIC: DCIS size >5 cm and core biopsy as the method of preoperative diagnosis. The finding that a larger DCIS size is more likely to be associated with invasive cancer is in agreement with the published literature[8, 11]. Yen et al.[8] also reported that, on multivariate analysis, patients diagnosed with DCIS or MIC by core biopsy were at increased risk for invasive cancer compared with patients diagnosed by excisional biopsy. It is likely a result of the documented problem of histologic underestimation of invasive disease by such percutaneous methods which sample only a small portion of the lesion. An excisional biopsy allows the pathologist to assess more of the lesion for diagnostic purposes. In addition, there are limitations on the quality and extent of pathologic material received for review from referring institutions. The majority of core-needle biopsies performed at our institution during the time period covered by this study used an 11-gauge Mammotome device. The core biopsy techniques performed at referring institutions were not explored.

Whether SLND should be performed routinely for all patients with a preoperative diagnosis of DCIS or MIC or for only certain subsets of patients has been debated. In one study of patients with DCIS, 5.7% had evidence of metastasis in their SLNs[6]. The authors concluded that SLND should be routinely used for DCIS patients to identify and correctly stage disease with undetected invasive disease. In a later report of 195 DCIS patients where 13% had evidence of SLN metastases, the same authors strongly recommended that SLND should become a routine part of surgical treatment for all DCIS patients[4]. However, because previous studies have reported the incidence of nodal positivity to be less than 3% in patients with DCIS, some clinicians have suggested selective use of SLND in DCIS patients based on type of biopsy, a palpable or mammographic mass, suspicion of microinvasion, multicentric disease, or the presence of high nuclear grade or necrosis[3, 5, 7]. Our clinical experience of detecting a low incidence of positive SLNs in patients with a diagnosis of DCIS or MIC and our studies of the predictors for SLN metastasis have led us to selective use of SLN node evaluation for such patients. We believe that routine SLND in all patients with DCIS or MIC is not warranted. Patients most likely to benefit from SLND at the time of breast surgery are those with DCIS size >5cm. Approximately 24% of patients with DCIS diagnosed by core biopsy will prove to have invasive cancer on final pathology and will then require SLN biopsy for axillary staging. Patients with DCIS who are scheduled for mastectomy should be considered for SLN biopsy at the time of mastectomy. Patients with DCIS or MIC diagnosed by core biopsy should be distinguished as higher risk for harboring invasive disease and discussion can be undertaken as to whether SLN biopsy should be performed at the time of lumpectomy. For those with DCIS >5 cm, SLN dissection should be considered because of a higher risk of finding a positive SLN or invasive cancer by final pathologic assessment. For those with DCIS ≤ 5 cm, SLN dissection should not be routinely performed at the time of lumpectomy. If invasive cancer is found by final pathologic assessment, the patient can then undergo SLN dissection for nodal staging. Our study has a few limitations, including the potential limitations inherent to any single-institutional, retrospective study. Notwithstanding, this study provides a valuable guide to physicians who treat patients with DCIS and MIC. In addition, we have not evaluated the long-term follow-up information for our cohort, and this information may be important. With these limitations in mind, we conclude that SLND in patients with a diagnosis of DCIS should be limited to patients who are planned for mastectomy or who have DCIS size >5 cm. Patients who have a core needle biopsy diagnosis of DCIS have a higher risk of harboring invasive breast cancer on final pathologic assessment of the primary tumor. This information can be used in preoperative counseling of patients with DCIS regarding the timing of SLN biopsy.

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Table 1

Univariate analysis of clinicopathologic factors and occurrence of SLN sentinel lymph node metastasis in patients with a preoperative (N = 624) diagnosis of DCIS or MIC

Characteristic	Positive SLN (N=40) N (%)	Negative SLN (N=584) N (%)	OR (95% CI)	P value
Age (y)				
>=50	19 (4.8)	377 (95.2)	Referent	
<50	21 (9.2)	207 (90.8)	2.0 (1.1–3.8)	.03
Race				
White	28 (6.2)	421 (93.8)	Referent	
Other	12 (7.0)	160 (93.0)	1.1 (0.6–2.3)	.74
Tumor location				
Outer quadrants	17 (5.7)	283 (94.3)	Referent	
Other quadrants	23 (7.1)	301(92.9)	1.3 (0.7–2.4)	.47
Palpable tumor				
Yes	11 (8.2)	124 (91.8)	Referent	
No	27 (5.7)	448 (94.3)	0.7 (0.3–1.4)	.30
Unknown	2 (14.3)	12 (85.7)		
DCIS size (cm)				
<=2 cm	3 (0.1)	306 (99.1)	Referent	
2–5 cm	12 (6.9)	163 (93.1)	7.5 (2.1–27.0)	.002
>5 cm	25 (17.9)	115 (82.1)	22.2 (6.6–74.9)	<0.0001
Method of preoperative diagnosis				
Excisional biopsy	2 (1.1)	186 (98.9)	Referent	
Core biopsy	38 (8.7)	398 (91.3)	8.9 (2.1–37.2)	.003
Final histologic type				
DCIS	6 (1.6)	38(98.4)	Referent	
MIC	3 (3.4)	86 (96.6)	2.2 (.5–9.0)	.27
Invasive cancer	31 (20.8)	118 (79.2)	16.6 (6.8–40.9)	<.0001
Necrosis				
Absent	7 (6.5)	109 (94.0)	Referent	
Present	33 (6.0)	475 (93.5)	1.1 (0.5–2.5)	.86
Type of DCIS				
Comedo	6 (4.1)	141 (95.9)	Referent	
Non-comedo	34 (7.1)	443 (92.9)	1.8(0.7–4.4)	.20
Estrogen receptor status				
Positive	26 (8.7)	273 (91.3)	Referent	
Negative	10 (8.1)	114 (91.9)	0.9 (0.4–2.0)	.83
Unknown	4 (2.0)	197 (98.0)		
Progesterone receptor status				
Positive	19 (7.8)	226 (92.2)	Referent	
Negative	16 (9.1)	160 (90.9)	1.2 (0.6–2.4)	.63

Characteristic	Positive SLN (N=40) N (%)	Negative SLN (N=584) N (%)	OR (95% CI)	P value
Unknown	5 (2.5)	198 (97.5)		
Histologic grade				
I	2 (6.1)	31 (93.9)	Referent	
II	17 (6.6)	228 (93.4)	1.1 (0.2–5.0)	.91
III	21 (6.3)	325 (93.7)		.96

DCIS: carcinoma in situ; MIC: microinvasive breast cancer; SLN: sentinel lymph node; OR: odds ratio; CI: confidence interval.

Table 2

Multivariate analysis of clinicopathologic factors and occurrence of SLN sentinel lymph node metastasis in patients with a preoperative (N = 624) diagnosis of DCIS or MIC

Characteristic	Positive SLN (N=40) N (%)	Negative SLN (N=584) N (%)	OR (95% CI)*	P value
Age (y)				
>=50	19 (4.8)	377 (95.2)	Referent	
<50	21 (9.2)	207 (90.8)	1.4 (0.6–2.9)	.43
DCIS size (cm)				
<=2 cm	3 (0.1)	306 (99.1)	Referent	
2–5 cm	12 (6.9)	163 (93.1)	6.8 (1.8–25.2)	.004
>5 cm	25 (17.9)	115 (82.1)	21.9 (6.3–76.7)	<.0001
Method of preoperative diagnosis				
Excisional biopsy	2 (1.1)	186 (98.9)	Referent	
Core biopsy	38 (8.7)	398 (91.3)	3.9 (0.9–17.5)	.08
Final histologic type				
DCIS	6 (1.6)	38(98.4)	Referent	
MIC	3 (3.4)	86 (96.6)	3.2 (0.8–13.6)	.11
Invasive cancer	31 (20.8)	118 (79.2)	16.9 (6.7–42.7)	<.0001

DCIS: carcinoma in situ; MIC: microinvasive breast cancer; SLN: sentinel lymph node; OR: odds ratio; CI: confidence interval.

*OR and 95% CI values were obtained from multivariate analysis with all variables significant in univariate analysis fitted simultaneously.

Table 3

Univariate analysis of clinicopathologic factors and occurrence of SLN sentinel lymph node metastasis in patients with a final (N = 475) diagnosis of DCIS or MIC

Characteristic	Positive SLN (N=9) N (%)	Negative SLN (N=486) N (%)	OR (95% CI)	P value
Age (y)				
>=50	3 (1.0)	319 (99.0)	Referent	
<50	6 (3.5)	167 (96.5)	3.6 (0.9–14.9)	.07
Race				
White	6 (1.8)	343 (98.2)	Referent	
Other	3 (2.3)	143 (97.7)	1.3 (0.3–5.2)	.73
Tumor location				
Outer quadrants	3 (1.3)	240 (98.7)	Referent	
Other quadrants	6 (2.4)	198 (97.6)	1.9 (0.5–7.6)	.38
Palpable tumor				
Yes	1 (1.0)	96 (99.0)	Referent	
No	8 (2.2)	359 (97.8)	2.1 (0.3–17.3)	.48
Unknown	0 (0.0)	6 (100.0)		
DCIS size (cm)				
<=2 cm	1 (0.4)	248 (99.6)	Referent	
2–5 cm	3 (2.3)	126 (97.7)	5.9 (0.6–57.4)	.13
>5 cm	5 (5.2)	92 (94.8)	13.4 (1.6–116.9)	.02
Method of preoperative diagnosis				
Excisional biopsy	2 (1.2)	(98.8)	Referent	
Core biopsy	7 (2.3)	(97.7)	1.9 (0.4–9.4)	.41
Final histologic type				
DCIS	6 (1.6)	398 (98.4)	Referent	
MIC	3 (3.4)	88 (96.6)	0.9 (0.1–7.0)	.89
Necrosis				
Absent	6 (1.6)	109 (94.0)	Referent	
Present	3 (3.1)	475 (93.5)	0.5 (0.1–2.1)	.35
Type of DCIS				
Comedo	2 (1.8)	112 (98.2)	Referent	
Non-comedo	7 (1.9)	374 (98.1)	1.1 (0.2–5.4)	.90
Estrogen receptor status				
Positive	4 (1.9)	213(98.1)	Referent	
Negative	3 (3.8)	78(96.2)	2.1 (0.4–9.4)	.35
Unknown	2 (1.1)	195(98.9)		
Progesterone receptor status				
Positive	3 (1.7)	182(98.3)	Referent	
Negative	3 (2.8)	108(97.2)	1.7 (0.3–8.4)	.54
Unknown	3 (1.6)	196(98.4)		

Characteristic	Positive SLN (N=9) N (%)	Negative SLN (N=486) N (%)	OR (95% CI)	P value
Histologic grade				
I	2 (3.9)	31 (93.9)	Referent	
II	4 (2.2)	228 (93.4)	0.6 (0.1–5.1)	.60
III	4 (1.5)	325 (93.7)	0.4 (0.04–3.6)	.40

DCIS: carcinoma in situ; MIC: microinvasive breast cancer; SLN: sentinel lymph node; OR: odds ratio; CI: confidence interval.

Table 4

Multivariate analysis of clinicopathologic factors and occurrence of SLN sentinel lymph node metastasis in patients with a final (N = 475) diagnosis of DCIS or MIC

Characteristic	Positive SLN (N=9) N (%)	Negative SLN (N=486) N (%)	OR (95% CI)*	P value
Age (y)				
>=50	3 (1.0)	319 (99.0)	Referent	
<50	6 (3.5)	167 (96.5)	3.2 (0.8–13.0)	.11
DCIS size (cm)				
<=2 cm	1 (0.4)	248 (99.6)	Referent	
2–5 cm	3 (2.3)	126 (97.7)	5.9 (0.6–57.4)	.13
>5 cm	5 (5.2)	92 (94.8)	13.4 (1.6–116.9)	.02

DCIS: carcinoma in situ; MIC: microinvasive breast cancer; SLN: sentinel lymph node; OR: odds ratio; CI: confidence interval.

*OR and 95% CI values were obtained from multivariate analysis with all variables significant in univariate analysis fitted simultaneously.

Table 5

Association between clinicopathologic factors and occurrence of invasive breast cancer in 624 patients with a preoperative diagnosis of DCIS or MIC

Characteristics	Invasive Cancer (N=149)	Univariate analysis		Multivariate analysis	
	N (%)	OR (95% CI)	P value	OR (95% CI)*	P value
Age (y)					
>=50	91 (23.0)	Referent			
<50	59 (25.4)	1.1 (0.8–1.7)	.49		
Race					
White	109 (24.3)	Referent			
Other	39 (22.7)	0.9 (0.6–1.4)	.68		
Tumor location					
Outer quadrants	72 (24.0)	Referent			
Other quadrants	77 (23.8)	1.0 (0.7–1.4)	.95		
Palpable tumor					
Yes	38 (28.2)	Referent			
No	108 (22.7)	0.8 (0.5–1.2)	.19		
Unknown	3 (21.4)				
DCIS size (cm)					
<=2 cm	60 (19.4)	Referent		Referent	
2–5 cm	46 (26.3)	1.5 (1.0–2.3)	.08	1.5 (0.9–2.3)	.08
>5 cm	43 (30.7)	1.8 (1.2–2.9)	.01	1.6 (1.02–2.6)	.04
Method of preoperative diagnosis					
Excisional biopsy	20 (10.6)	Referent		Referent	
Core biopsy	129 (29.6)	3.5 (2.1–5.9)	<.001	3.4 (2.0–5.7)	<.001
Preoperative histologic type					
DCIS	126 (23.3)	Referent			
MIC	23 (27.7)	1.3 (0.8–2.1)	.38		
Necrosis					
Absent	18 (15.5)	Referent		Referent	
Present	131 (25.8)	1.9 (1.1–3.2)	.02	1.6 (0.9–2.7)	.11

Characteristics	Invasive Cancer (N=149)	Univariate analysis		Multivariate analysis	
	N (%)	OR (95% CI)	P value	OR (95% CI)*	P value
Type of DCIS					
Comedo	33 (22.5)	Referent			
Non-comedo	116 (24.3)	1.1 (0.7–1.7)	.64		
Estrogen receptor status					
Positive	87 (29.1)	Referent			
Negative	45 (36.3)	1.4 (0.9–2.2)	.15		
Unknown	17 (8.5)				
Progesterone receptor status					
Positive	65 (26.5)	Referent			
Negative	67 (28.9)	1.1 (0.8–1.7)	.57		
Unknown	17 (11.6)				
Histologic grade					
I	7(21.2)	Referent			
II	73 (28.3)	1.5 (0.6–3.5)	.39		
III	69 (20.7)	1.0 (0.4–2.3)	.95		

DCIS: carcinoma in situ; MIC: microinvasive breast cancer; SLN: sentinel lymph node; OR: odds ratio; CI: confidence interval.

*OR and 95% CI values were obtained from multivariate analysis with all variables significant in univariate analysis fitted simultaneously.