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# Predictors of Invasive Breast Cancer in Patients with an Initial Diagnosis of Ductal Carcinoma in Situ: A Guide to Selective Use of Sentinel Lymph Node Biopsy in Management of Ductal Carcinoma in Situ

Tina WF Yen, MD, Kelly K Hunt, MD, FACS, Merrick I Ross, MD, FACS, Nadeem Q Mirza, MD, MPH, Gildy V Babiera, MD, FACS, Funda Meric-Bernstam, MD, FACS, S Eva Singletary, MD, FACS, W Fraser Symmans, MD, Sharon H Giordano, MD, MPH, Barry W Feig, MD, FACS, Frederick C Ames, MD, FACS, Henry M Kuerer, MD, PhD, FACS

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**BACKGROUND:** The role of sentinel lymph node biopsy (SLNB) in patients with an initial diagnosis of ductal carcinoma in situ (DCIS) has not been well defined. The purpose of our study was to determine when the risk of finding invasive disease on final pathology in patients with an initial diagnosis of DCIS was sufficiently high to justify use of SLNB.

**STUDY DESIGN:** The records of 398 consecutive patients from our prospective database with an initial diagnosis of DCIS, treated between July 1999 and December 2002, were analyzed. Associations between clinical and pathologic factors and patient selection for SLNB and outcomes were analyzed for significance using univariate and multivariate analyses.

**RESULTS:** Of the 398 patients, 80 (20%) were found to have invasive disease on final pathology. Multivariate analysis revealed 4 independent predictors of invasive cancer on final pathology: 55 years of age or younger (odds ratio [OR], 2.19;  $p = 0.024$ ), diagnosis by core-needle biopsy (OR, 3.76;  $p = 0.006$ ), mammographic DCIS size of at least 4 cm (OR, 2.92;  $p = 0.001$ ), and high-grade DCIS (OR, 3.06;  $p = 0.002$ ). A total of 141 patients (35%) underwent SLNB as a component of their initial operation. Multivariate analysis revealed that the presence of comedonecrosis (OR, 2.69;  $p = 0.007$ ) and larger mammographic DCIS size (OR, 1.18;  $p = 0.0002$ ) were independent predictors of patients' undergoing SLNB. Of these 141 patients, 103 (73%) were diagnosed by core-needle biopsy, 42 (30%) had invasive disease on final pathology, and 14 (10%) had a positive sentinel lymph node: 12 (86%) by hematoxylin and eosin staining and 2 by immunohistochemistry. The only independent predictor of a positive SLN was the presence of a palpable tumor (OR, 4.28,  $p = 0.042$ ). Of these 14 patients with a positive sentinel node, only 11 (79%) had invasive cancer on final pathology.

**CONCLUSIONS:** SLNB should not be performed routinely for all patients with an initial diagnosis of DCIS. Risks and benefits of SLNB should be discussed with patients who are younger, are diagnosed by core-needle biopsy, or have large or high-grade DCIS. (*J Am Coll Surg* 2005;200:516–526. © 2005 by the American College of Surgeons)

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Ductal carcinoma in situ (DCIS) is a heterogeneous disease that currently accounts for approximately 20% of all

screening-detected breast cancers.<sup>1</sup> This disease is characterized by proliferation of neoplastic ductal epithelial cells that are confined to the basement membrane of mammary ducts. By definition, DCIS is not an invasive malignancy and does not have the ability to metastasize to regional lymph nodes. Historically, fewer than 1% to 2% of patients with DCIS who have undergone axillary lymph node dissection (ALND) have had axillary metastases detected by conventional hematoxylin and eosin (H&E) staining.<sup>2-5</sup> Breast cancer-specific mortality rate for patients with

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From the Departments of Surgical Oncology (Yen, Hunt, Ross, Mirza, Babiera, Meric-Bernstam, Singletary, Feig, Ames, Kuerer), Pathology (Symmans), and Breast Medical Oncology (Giordano), The University of Texas MD Anderson Cancer Center, Houston, TX.

Correspondence address: Henry M Kuerer, MD, PhD, Department of Surgical Oncology, Unit 444, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

**Abbreviations and Acronyms**

ALND	= axillary lymph node dissection
DCIS	= ductal carcinoma in situ
H&E	= hematoxylin and eosin
OR	= odds ratio
SLN	= sentinel lymph node
SLNB	= sentinel lymph node biopsy

DCIS is only 1% to 2%.<sup>6-9</sup> The explanation for breast cancer deaths in patients with DCIS is that the area of DCIS harboring invasive disease is too small to be detected on routine pathologic evaluation. Use of ALND is not indicated in patients with pure DCIS, given the low incidence of nodal metastases and the significant morbidity associated with this procedure.

As an increasing number of patients are being diagnosed with breast malignancies by percutaneous biopsy techniques, the limited sampling inherent in these techniques leads to the histologic underestimation of invasive disease. Today, rates of identifying invasive cancer at operation in patients initially diagnosed with DCIS by core-needle biopsy and vacuum-assisted biopsy devices are 16% to 35% and 0% to 19%, respectively.<sup>10-15</sup> When the clinical and radiologic evidence is suspicious for invasive disease in a patient with a diagnostic biopsy revealing DCIS, treatment options must be individualized. It can be argued that some type of nodal staging should be considered in the subset of patients with DCIS who are at increased risk for harboring invasive disease and are at increased risk for axillary metastases. Given the reliability and relatively low morbidity rate associated with lymphatic mapping and sentinel lymph node biopsy (SLNB) for invasive breast cancer, this procedure has been considered in the surgical management of patients with an initial diagnosis of DCIS.

To our knowledge, five studies evaluating SLNB in patients with DCIS have been reported to date.<sup>16-20</sup> The studies reported sentinel lymph node (SLN) metastasis rates ranging from 1.3% to 13%, which includes SLNs evaluated by both H&E staining and immunohistochemistry and patients found to have invasive disease on reevaluation of the primary tumor. This finding is discordant with the historical rate of 1% to 2% axillary involvement in patients undergoing ALND and with lymph node assessment by conventional H&E staining.<sup>2-5</sup> If only SLNs found to be positive by H&E are included, then the SLN metastasis rate in the five published studies falls to 2% to 7%. The authors of the studies offered different recommendations

about use of SLNB in patients with an initial diagnosis of DCIS, ranging from selective use to routine use in all patients.<sup>16-20</sup>

On the basis of findings from these studies of SLNB in patients with DCIS, the 2001 Consensus Conference on the role of SLNB in carcinoma of the breast<sup>21</sup> concluded that SLNB might be indicated for patients with DCIS detected as a palpable mass or DCIS with extensive microcalcifications, as the risk of invasive disease is thought to be higher in such patients. The current National Comprehensive Cancer Network guidelines<sup>22</sup> state that SLNB could be considered in patients with an initial diagnosis of DCIS who are to be treated with mastectomy or with excision in an anatomic area that could compromise the performance of SLNB in the future. Morrow and colleagues<sup>23</sup> also advocate a selective approach to SLNB in patients with DCIS, concluding that SLNB should be considered in patients with large DCIS lesions necessitating mastectomy, as occult invasive disease may be present and SLNB cannot be performed after a mastectomy.

The dilemma about SLNB in patients initially diagnosed with DCIS resides in determining the predictors of invasive disease in these patients. Historically, risk factors reportedly associated with invasive disease have included large tumors, high-grade tumors, tumors with comedo-type necrosis, and presence of a palpable mass or mass that is appreciated by imaging studies.<sup>14,24-30</sup> As long as the actual predictors of invasive cancer in patients with an initial diagnosis of DCIS remain to be elucidated, the role of SLNB in this group of patients will remain undefined. The purpose of our study was to determine when the risk of finding invasive disease on final pathology evaluation in patients with the initial diagnosis of DCIS was sufficiently high to justify use of SLNB.

**METHODS**

After approval by the institutional review board of The University of Texas MD Anderson Cancer Center, the records of all 462 consecutive patients with an initial diagnosis of DCIS by core-needle biopsy or excisional biopsy treated at our institution between July 1999 and December 2002 were obtained from a prospective database and analyzed. All prereferral pathology slides were reviewed by pathologists at MD Anderson Cancer Center. Patients were excluded if they did not undergo operation at MD Anderson. At our institution, core-needle

biopsies were performed with either an 11- or 14-gauge Mammotome device (Ethicon Corp).

Associations between clinical and pathologic factors and these outcomes were analyzed: presence of invasive breast cancer, use of SLNB, and presence of a positive SLN. Clinical factors examined included patient age, method of initial diagnosis, presence of a palpable tumor at initial presentation, mammographic DCIS size (defined by the extent of microcalcifications), and type of operation. Pathologic factors evaluated included DCIS size, histologic grade, presence of comedonecrosis, presence of invasive cancer in the resected specimen, and the presence of metastatic disease in the SLNB specimens. Invasive disease included DCIS with microinvasion, defined as invasion  $\leq 0.1$  cm in greatest dimension.<sup>31</sup> All SLNB specimens were classified according to the sixth edition of the *AJCC Cancer Staging Manual*.<sup>31</sup>

#### Technique of intraoperative lymphatic mapping and SLNB

Our technique of SLNB has been described previously.<sup>32,33</sup> Briefly, intraoperative lymphatic mapping was performed with injections of technetium 99m-labeled sulfur colloid alone or in combination with lymphazurin blue dye. Lymphoscintigraphy was performed by injecting filtered technetium 99m sulfur colloid into the breast parenchyma surrounding the tumor or the biopsy cavity, either the day of operation (0.5 mCi) or the day before operation (2.5 mCi). With the patient under general anesthesia in the operating room, 5 mL 1% isosulfan blue dye (Lymphazurin; US Surgical) was injected peritumorally, and the breast was massaged for 5 minutes. A hand-held gamma probe (NeoProbe 2000; US Surgical) was used to scan the axilla transcutaneously and to identify the most radioactive area. An axillary incision was then made over this "hot spot," and the SLNs were identified as those with blue dye uptake, radiotracer uptake (more than twice the background count), or both.

#### Pathologic evaluation of SLNs

SLNs were serially sectioned at 2- to 3-mm intervals and were entirely submitted for routine tissue processing and embedding into paraffin blocks. The tissue in each paraffin block was sectioned at 4- to 5- $\mu$ m intervals to produce 5 serial sections. Sections 1, 2, and 4 were evaluated by routine H&E staining. If no metastasis was present at these three levels, then level 3 was subjected to immunohistochemical staining with an anticytokeratin

antibody cocktail consisting of AE1/AE3 (Chemicon), CAM 5.2 (Becton Dickinson), MNF 116 (Dako), and ZYM 5.2 (Zymed).<sup>34</sup>

#### Statistical analysis

Descriptive statistical techniques were used to evaluate frequency distribution. The differences in the distribution of categorical variables were analyzed using the Pearson chi-square test or Fisher's exact test, and the differences between continuous variables were tested using the Mann-Whitney U test. The logistic regression model was used for multivariate analysis. Covariates were selected in a forward stepwise manner, with the use of the maximum likelihood ratio. All p values  $\leq 0.05$  were considered statistically significant. All p values are two-sided. SPSS 11.5 software package (SPSS Inc) was used for statistical analysis.

## RESULTS

Of the 462 patients with an initial diagnosis of DCIS by core-needle biopsy or excisional biopsy, 64 patients did not undergo operation at MD Anderson and were excluded from analysis. Of these 64 patients, 38 were seen at MD Anderson for a second opinion, 19 underwent definitive operation before presentation to our institution, 6 were not seen after initial evaluation, and 1 refused the operation. The study group comprised 398 patients. Median age of patients at the time of diagnosis was 54 years (range 24 to 89 years) and median mammographic DCIS size was 2.5 cm (range 0.3 to 13 cm). All patients underwent operation at MD Anderson and had negative surgical margins.

#### Clinicopathologic predictors of invasive breast cancer

Initial diagnosis of DCIS was made by percutaneous core-needle biopsy in 260 patients (65%) and by excisional biopsy in 138 (35%). Of the 260 who were diagnosed with DCIS by core-needle biopsy, 66 (25%) had invasive cancer on final pathology review. Of the 138 who were diagnosed with DCIS by excisional biopsy, 14 (10%) had invasive cancer on final pathology review. Of 398 patients with an initial diagnosis of DCIS, a total of 80 patients (20%) had invasive disease on final pathology review, 66 with invasive breast cancer and 14 with DCIS with microinvasion. Of these 80 patients, 58 (72%) underwent axillary evaluation at the time of their initial opera-

**Table 1.** Univariate Analysis of Predictors of Invasive Breast Cancer in Patients with an Initial Diagnosis of Ductal Carcinoma in Situ

Clinicopathologic feature	Findings on final pathologic evaluation		p Value*
	DCIS only (n = 318)	Invasive cancer (n = 80)	
Median age at diagnosis (y)	55.5	50.4	0.005
Range	24–89	29–75	
Method of diagnosis, n (%)			<0.001
Core-needle biopsy	194 (61)	66 (82)	
Excisional biopsy	124 (39)	14 (18)	
Palpable lesion, n (%)	42 (13)	15 (19)	0.182
Median mammographic DCIS size (cm)	2.0	4.5	<0.001 <sup>‡</sup>
Range <sup>†</sup>	0.3–13.0	0.3–12.0	
Tumor grade, n (%)			<0.001
1	26 (8)	0	
2	145 (45)	20 (25)	
3	147 (46)	60 (75)	
Median pathologic DCIS size (cm)	1.5	2.2	0.127 <sup>‡</sup>
Range <sup>§</sup>	(0.04–10.0)	(0.2–10.0)	
Comedonecrosis, n (%)			0.001 <sup>  </sup>
Present	213 (67)	71 (89)	
Absent	88 (28)	8 (10)	
Unknown	17 (5)	1 (1)	
Type of final operation, n (%)			<0.001
Segmental mastectomy	169 (53)	21 (26)	
Total mastectomy	149 (47)	59 (74)	

\*Calculated by Pearson chi-square test unless otherwise noted.

<sup>†</sup>Based on 196 patients with DCIS and 56 patients with invasive cancer on final pathology review for whom mammographic DCIS size was known.

<sup>‡</sup>Calculated by Mann-Whitney U test.

<sup>§</sup>Based on 230 patients with DCIS and 52 patients with invasive cancer on final pathology review for whom pathologic DCIS size was known.

<sup>||</sup>Excludes patients with unknown values.

DCIS, ductal carcinoma in situ.

tion at MD Anderson and were spared a subsequent operation for axillary staging.

Univariate analysis of clinicopathologic predictors of invasive breast cancer in patients with an initial diagnosis of DCIS is summarized in Table 1. Multivariate analysis using all six significant univariate variables revealed four independent predictors of invasive cancer on final pathology review: younger age, diagnosis by core-needle biopsy, larger mammographic DCIS size, and high-grade DCIS tumor (Table 2).

### Clinicopathologic predictors of performing SLNB in patients with an initial diagnosis of DCIS

Of the 398 patients in the study, at the time of initial operation at our institution, 253 (64%) did not undergo axillary staging, and 141 (35%) underwent SLNB (Table 3). The remaining 4 patients (1%) were excluded from further analysis as they underwent SLNB before evaluation at MD Anderson. Of the 141 patients who underwent SLNB with their initial operation at MD Anderson, 42 (30%) had invasive cancer

**Table 2.** Multivariate Analysis of Predictors of Invasive Breast Cancer in Patients with Initial Diagnosis of Ductal Carcinoma in Situ

Independent predictors of invasive cancer	$\beta$ Coefficient	Odds ratio	95% CI	p Value
Age $\leq$ 55 y	0.782	2.19	1.11–4.32	0.024
Core-needle biopsy	1.324	3.76	1.46–9.63	0.006
Mammographic DCIS size $\geq$ 4 cm	1.073	2.92	1.51–5.66	0.001
Grade 3 DCIS	1.119	3.06	1.49–6.30	0.002

DCIS, ductal carcinoma in situ.

**Table 3.** Factors Associated with Performing Sentinel Lymph Node Biopsy in Patients with Initial Diagnosis of Ductal Carcinoma in Situ\*

Clinicopathologic feature	No axillary staging (n = 253)	SLNB (n = 141)	p Value <sup>†</sup>
Median age at diagnosis (y)	55.4	51.9	0.030
Range	24–89	29–79	
Method of diagnosis, n (%)			0.018
Core-needle biopsy	155 (61)	103 (73)	
Excisional biopsy	98 (39)	38 (27)	
Palpable lesion, n (%)	32 (13)	25 (18)	0.169
Median mammographic DCIS size (cm)	2	4	<0.001 <sup>‡</sup>
Range <sup>§</sup>	0.3–11	0.3–13	
Tumor grade, n (%)			<0.001
1	23 (10)	2 (1)	
2	115 (45)	50 (36)	
3	115 (45)	89 (63)	
Median pathologic DCIS size (cm)	1.2	2	<0.001 <sup>‡</sup>
Range <sup>  </sup>	0.04–10	0.15–10	
Comedonecrosis, n (%)			0.023 <sup>¶</sup>
Present	168 (66)	112 (80)	
Absent	70 (28)	26 (18)	
Unknown	15 (6)	3 (2)	
Final pathology, n (%)			<0.001
Invasive cancer	27 (11)	39 (28)	
DCIS with microinvasion	11 (4)	3 (2)	
DCIS	215 (85)	99 (70)	
Type of final operation, n (%)			<0.001
Segmental mastectomy	157 (62)	31 (22)	
Total mastectomy	96 (38)	110 (78)	

\*Excludes four patients who had SLNB at another institution.

<sup>†</sup>Calculated by Pearson chi-square test unless otherwise noted.

<sup>‡</sup>Calculated by Mann-Whitney U test.

<sup>§</sup>Based on 151 patients who did not undergo axillary staging and 100 patients who underwent SLNB for whom mammographic DCIS size was known.

<sup>||</sup>Based on 177 patients who did not undergo axillary staging and 103 patients who underwent SLNB for whom pathologic DCIS size was known.

<sup>¶</sup>Excludes patients with unknown values.

DCIS, ductal carcinoma in situ; SLNB, sentinel lymph node biopsy.

on final pathology review. Thirty-seven patients had invasive ductal carcinoma, 3 had DCIS with microinvasion, 1 had invasive ductal and lobular carcinoma, and 1 had invasive lobular carcinoma. Of these 141 patients who underwent SLNB, 103 (73%) were diagnosed with DCIS by core-needle biopsy, and 110 (78%) underwent total mastectomy as their final operation. Of the 110 patients who underwent total mastectomy and SLNB for an initial diagnosis of DCIS, 33 (30%) were found to have invasive cancer on final pathology review and so were spared ALND for axillary staging purposes.

Univariate analysis of clinicopathologic predictors of performing SLNB in patients with an initial diagnosis of DCIS is summarized in Table 3. Multivariate analysis revealed that comedonecrosis (odds ratio [OR], 2.69,

95% CI, 1.30–5.54,  $p = 0.007$ ) and larger mammographic DCIS size (OR, 1.18, 95% CI, 1.06–1.30,  $p = 0.002$ ) were independent predictors of patients' undergoing SLNB.

#### Clinicopathologic predictors of a positive SLN in patients undergoing SLNB for an initial diagnosis of DCIS

Of the 141 patients who underwent SLNB with initial operation for presumed DCIS, 14 (10%) had a positive SLN (Table 4). Of these 14 patients, 11 (79%) had invasive cancer on final pathology review, and 11 (79%) underwent total mastectomy as their final operation. A total of 45 SLNs were retrieved from these 14 patients (median, 2.5 SLNs per patient; range 1 to 8 SLNs). Eighteen SLNs (40%) were pos-

**Table 4.** Pathologic Status of the 14 Patients Who Had a Positive Sentinel Lymph Node

Patient No.	Highest-stage disease on final pathology review (size, cm)	ER/PR status	Final operation	SLN status*	Completion ALND? Timing Nodal status <sup>†</sup>	Adjuvant treatment
1	DCIS (UNK)	UNK	SM	pN1mi	No	Chemotherapy and TAM
2	DCIS (2.1)	UNK	TM	pN1mi	No-declined	Chemotherapy
3	DCIS with microinvasion (UNK)	ER- PR+	TM	pN1mi	No	Anastrozole
4	IDC (0.7)	UNK	SM	pN1mi	No-declined	Declined all further treatment options
5	IDC (0.9)	ER+ PR+	TM	pN1mi	No-declined	Chemotherapy
6	IDC (0.2)	ER- PR-	TM	pN1mi	No	Chemotherapy
7	IDC/ILC (0.7)	ER+ PR+	TM	pN0(i+)	No-declined	TAM
8	IDC (2.2)	ER- PR-	SM	pN1a	No	Chemotherapy and axillary radiation therapy
9	IDC (0.6)	ER- PR-	TM	pN1mi	No-declined	Chemotherapy
10	DCIS (8.0)	UNK	TM	pN1mi	Yes Subsequent Negative	TAM and anastrozole
11	IDC (multifocal)	ER+ PR+	TM	pN1mi	Yes Concurrent Negative	TAM
12	IPC (1.5)	ER+ PR+	TM	pN1a	Yes Concurrent Negative	Chemotherapy and TAM
13	ILC (multifocal)	ER+ PR-	TM	pN1a	Yes Subsequent Negative	Chemotherapy and anastrozole
14	IDC (7.0)	ER+ PR+	TM	pN0(i+)	Yes Concurrent 1/15 nodes positive pN1a*	Chemotherapy and anastrozole

\*Staging per *AJCC Cancer Staging Manual*, 6<sup>th</sup> ed.<sup>31</sup>

<sup>†</sup>Column denotes whether a completion ALND was performed (yes/no). If a completion ALND was performed, the timing of the ALND (concurrent/subsequent) and the nodal status of the ALND specimen (negative/positive) are listed.

ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ; ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IPC, invasive papillary carcinoma; PR, progesterone receptor; SLN, sentinel lymph node; SM, segmental mastectomy; TAM, tamoxifen; TM, total mastectomy; UNK, unknown.

itive. Of these 14 patients, 12 (86%) had SLNs that were positive by H&E staining (3 pN1a, 9 pN1mi), and 2 had SLNs that were positive by immunohistochemistry alone (pN0 [i+]).

Nine of the 14 patients did not undergo completion ALND. Five of these patients declined completion ALND; one received axillary radiation therapy; and in the remaining three, multidisciplinary team recommendations were to not pursue completion ALND. Patient 1 had DCIS on final pathology review and 1 of 2 SLNs revealed a single

cluster of a few cells that were positive by H&E staining. Patient 3 had DCIS with microinvasion and 2 SLNs that had clusters of tumor cells that were positive by immunohistochemistry; one of these SLNs was also positive by H&E staining. Patient 6 had a 0.2-cm invasive ductal carcinoma and 1 SLN that was positive by H&E staining and measured 2 mm. Seven other SLN specimens were negative for metastasis. Of the 5 patients who underwent completion ALND (3 concurrent, 2 subsequent), only 1—patient 14, who had invasive ductal carcinoma on final pathology

**Table 5.** Predictors of a Positive Sentinel Lymph Node in Patients with an Initial Diagnosis of Ductal Carcinoma in Situ Who Underwent Sentinel Lymph Node Biopsy

Clinicopathologic feature	Negative SLNB (n = 127)	Positive SLNB (n = 14)	p Value*
Median age at diagnosis (y)	53.6	49.1	0.056
Range	35–79	29–67	
Palpable lesion, n (%)	19 (15)	6 (43)	0.009
Median mammographic DCIS size (cm)	3.5	5.75	0.031 <sup>‡</sup>
Range <sup>†</sup>	0.3–12 cm	1.3–13 cm	
Tumor grade, n (%)			0.652 <sup>§</sup>
1	2 (1)	0	
2	44 (35)	6 (43)	
3	81 (64)	8 (57)	
Median pathologic DCIS size (cm)	2	5	0.376 <sup>‡</sup>
Range <sup>  </sup>	0.15–10	0.3–8	
Comedonecrosis, n (%)			0.794 <sup>¶</sup>
Present	101 (80)	11 (79)	
Absent	23 (18)	3 (21)	
Unknown	3 (2)	0	
Final pathology, n (%)			0.001 <sup>§</sup>
Invasive cancer	29 (23)	10 (71)	
DCIS with microinvasion	2 (1)	1 (7)	
DCIS	96 (76)	3 (21)	
Type of final operation, n (%)			0.958
Segmental mastectomy	28 (22)	3 (21)	
Total mastectomy	99 (78)	11 (79)	

\*p value calculated by Pearson chi-square test unless otherwise noted.

<sup>†</sup>Based on 90 patients with a negative SLNB and 16 patients with a positive SLNB for whom mammographic DCIS size was known.

<sup>‡</sup>p value calculated by Mann-Whitney U test.

<sup>§</sup>p value calculated by Fisher's exact test.

<sup>||</sup>Based on 96 patients with a negative SLNB and 7 patients with a positive SLNB for whom pathologic DCIS size was known.

<sup>¶</sup>Excludes patients with unknown values.

DCIS, ductal carcinoma in situ; SLNB, sentinel lymph node biopsy.

review—had an additional positive axillary node identified. Of the 14 patients with positive SLNs, 5 received chemotherapy, 4 received hormonal therapy, 4 received both chemotherapy and hormonal therapy, and 1 refused systemic treatment.

All three patients with pure DCIS and a positive SLN had micrometastatic disease (pN1mi). Patient 1 had grade 1 to 2 solid and cribriform DCIS without necrosis on core-needle biopsy and segmental mastectomy. She received chemotherapy and tamoxifen and did not undergo completion ALND. Patient 2 had grade 2 solid and cribriform DCIS with necrosis on needle-localization excisional biopsy and had no residual tumor in the subsequent total mastectomy specimen. She underwent chemotherapy and declined completion ALND. Patient 10 had grade 2 solid, cribriform, and papillary DCIS with necrosis on core biopsy and total mastectomy. One of two SLNB specimens revealed a single cluster of tumor cells that was positive by H&E staining. She underwent completion ALND (18

nodes removed; all negative), took tamoxifen, and was then switched to anastrozole because of vaginal bleeding from endometrial polyps.

Univariate analysis of clinicopathologic predictors of a positive SLN is summarized in Table 5. Multivariate analysis revealed that the only independent predictor of a positive SLNB was the presence of a palpable tumor (OR, 4.28, 95% CI, 1.05–17.41,  $p = 0.042$ ).

#### Patients undergoing total mastectomy without axillary staging

A total of 42 patients with an initial diagnosis of DCIS underwent total mastectomy without axillary staging. Six (14%) had evidence of invasive cancer on final pathology review. One patient was found to have a 1.5-mm invasive ductal carcinoma in the total mastectomy specimen. No axillary staging or further treatment was performed. The remaining five patients had DCIS with microinvasion on final pathology review. Four patients

declined subsequent axillary staging and one had undergone a previous ALND for an ipsilateral invasive breast cancer; one received chemotherapy followed by tamoxifen, two received tamoxifen alone, and two received no systemic treatment.

### Patient outcomes

At a median followup time of 13 months (range 1 week to 38 months), 392 of the 398 patients were without evidence of disease. One patient had an in-breast recurrence of DCIS while on adjuvant tamoxifen therapy, 18 months after undergoing segmental mastectomy and radiation therapy. One patient was not seen in followup after undergoing an operation for DCIS. The remaining four patients had invasive cancer on final pathology review. Of these four patients, one recurred with the development of distant metastases despite chemotherapy and bone marrow transplantation; two had positive SLNs and were to complete chemotherapy before completion ALND; and one had a positive SLN and positive tumor margins after undergoing a segmental mastectomy but declined further therapy.

### DISCUSSION

In our study, we found that 20% of patients with an initial diagnosis of DCIS had invasive disease—either invasive breast cancer or DCIS with microinvasion—on final pathology review. By comparison, the studies by Cox and colleagues<sup>18</sup> and Brinkmann and colleagues<sup>20</sup> showed that 10% to 14% of patients with an initial diagnosis of DCIS were found to have invasive cancer after final pathology review. The higher incidence of invasive disease in our study, although in accordance with other previous studies,<sup>24,28,35</sup> may be attributed in part to limited sampling and histologic underestimation of invasive disease, given that more patients in our study (65%) were initially diagnosed with percutaneous biopsy techniques than in Cox's study (35%). Another possible contributing factor is that many of our patients were referred from other institutions and had only a select number of slides available for review by our pathologists to yield a diagnosis. We do not know how prereferral excisional biopsy specimens were evaluated initially at referring institutions. At our institution, the tumor is mapped out radiologically in the specimen and entirely submitted for histopathologic evaluation in DCIS patients to rule out microinvasive disease.

Multivariate analysis revealed four independent pre-

dictors of invasive cancer in patients with an initial diagnosis of DCIS: younger age, diagnosis by core-needle biopsy, large mammographic DCIS size, and high-grade tumor. The finding that younger age was a predictor of invasive cancer is explained by the fact that younger age is also associated with other adverse clinical factors for invasive disease, including higher tumor grade, presence of necrosis, more extensive disease, and clinical rather than mammographic findings on presentation.<sup>36</sup> The finding that patients diagnosed with DCIS by core-needle biopsy were at increased risk for invasive cancer, compared with those diagnosed by excisional biopsy, is likely a result of the documented problem of histologic underestimation of invasive disease by such percutaneous methods, and the 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. In support of our finding, diagnosis by core-needle biopsy was also a significant predictor of invasive disease in the study by Brinkmann and colleagues.<sup>20</sup> The findings that larger tumor size and high-grade tumors were predictors of invasive cancer are in agreement with the published literature.<sup>28,29</sup> Further analysis revealed that mammographic DCIS size and type of final operation were interrelated. The median mammographic size of DCIS of patients undergoing segmental mastectomy was 1.5 cm (range 0.3 to 8.0 cm); the median mammographic size of DCIS of patients ultimately undergoing total mastectomy was 4.0 cm (range 0.3 to 13.0 cm). Patients with smaller mammographic DCIS size were more likely to undergo segmental mastectomy and have no evidence of invasive disease on final pathology review, but patients with larger tumors on mammography were more likely to require total mastectomy for negative margins and were more likely to have invasive cancer on final pathology review. In our study, presence of a clinically palpable mass and presence of comedonecrosis were not predictors of invasive cancer; presence of comedonecrosis was significant on univariate analysis but not on multivariate analysis, probably because high-grade tumors and presence of comedonecrosis are interrelated. Importantly, of the 80 patients with invasive cancer on final pathology review, 58 (72%) underwent axillary evaluation at the

time of their initial operation and were spared a subsequent operation for axillary staging purposes.

In addition, we found that 35% of patients underwent SLNB with their initial operation; 30% of these patients had invasive cancer on final pathology review. Multivariate analysis revealed two independent predictors of performing SLNB in patients with an initial diagnosis of DCIS: large mammographic DCIS size and presence of comedonecrosis. We assume that patients were offered SLNB because their surgeons felt that they were at risk for invasive disease. Our finding indicates that surgeons concur with findings in the literature showing that patients with DCIS tumors that are large or display comedonecrosis are at increased risk for associated invasive disease.<sup>24-29</sup>

Although our numbers are small (14 [10%] of patients who underwent SLNB had a positive SLN), the only independent predictor of a positive SLN was presence of a palpable tumor. Of the 14 patients with a positive SLN, 12 had SLNs that were positive by H&E staining. Eleven (79%) had invasive cancer on final pathology review, and 5 underwent completion ALND. Only one patient with invasive cancer on final pathology review had additional metastases (in a single node) identified on ALND. Of the 99 patients with pure DCIS who underwent SLNB, only 3 (3%) had a positive SLN, which is in agreement with the historical literature. All three patients with pure DCIS and a positive SLN had micrometastatic disease (pN1mi). All three received systemic therapy and one underwent completion ALND that did not reveal any additional axillary metastases. Despite extensive pathologic evaluation of the primary tumor revealing no evidence of invasive cancer, we treated these patients systemically as we believe that patients with a positive SLN on H&E staining should be considered to have occult invasive disease and should be treated according to the standard of care for node-positive invasive cancers. This is the same rationale that Cody and Van Zee<sup>37</sup> propose and is presumably the same logic used in a study by Intra and colleagues<sup>19</sup> as all seven patients with metastatic SLNs in this study received adjuvant systemic treatment. The decision to undergo completion ALND or to receive chemotherapy or hormonal therapy when only micrometastases are identified in an SLN in the absence of detectable invasive breast cancer is controversial and complex for both the patient and her multidisciplinary clinical team. In the absence of longterm prospective data, decisions in this particular

clinical scenario must be individualized and made only after careful discussions in a multidisciplinary setting.

The significance of nodal micrometastatic disease (pN1mi) in DCIS is unknown. In invasive breast cancer, this is a subject of ongoing controversy,<sup>38</sup> although presence of micrometastatic disease may be associated with decreased survival.<sup>37,39-43</sup> More definitive answers will be obtained once the results of the American College of Surgeons Oncology Group Z0011 and National Surgical Adjuvant Breast and Bowel Project B-32 studies are published. Given the natural history of DCIS, patients with SLNs detected only by immunohistochemistry are probably at little or no risk of distant metastases or death from their disease. Treatment with completion ALND or systemic chemotherapy is unlikely to improve on the 98% cure rate with operation. Lara and colleagues<sup>44</sup> recently addressed this issue by reviewing 102 patients with DCIS who underwent resection of their primary tumor and negative ALND between 1974 and 1992. Axillary specimens were resected and subjected to immunohistochemical staining. Thirteen patients (13%) had micrometastases identified by immunohistochemistry. At 10 to 28 years of followup, 87 patients (85%) were without evidence of disease, and 25 (15%) had died of causes unrelated to breast cancer. Recurrence rate was 12%, but none of the patients with recurrence had evidence of micrometastases by immunohistochemical evaluation. In this study, micrometastases detected by immunohistochemistry did not identify patients with invasive disease, predict disease recurrence, or influence survival. In light of these findings and the natural history of DCIS, several investigators concluded that our ability to recognize metastatic disease may now exceed our understanding of its clinical relevance, so these investigators did not advocate systemic treatment in patients with micrometastases given side effects, risks, morbidity, and minimal treatment gain associated with such treatment.<sup>39,45,46</sup>

The possibility that immunohistochemical detection of cells in SLNs may represent not metastatic disease but passive transport of dislocated epithelial cells to the SLN after an invasive preoperative maneuver remains controversial, with unclear clinical implications.<sup>47,48</sup> Tamhane and colleagues<sup>49</sup> recently evaluated the axillary lymph nodes in 26 patients with DCIS diagnosed by core or open biopsy who underwent mastectomy. Final pathology review revealed no invasive cancer. Average number of lymph nodes per specimen was five. None was positive by H&E staining, but 6

patients (23%) had immunohistochemically detected positive nodes. In comparison, the lymph nodes of seven patients who underwent prophylactic mastectomy without previous manipulation of the breast demonstrated no cytokeratin-positive cells. At a mean followup of 5 years in the patients with DCIS, no patient developed a local recurrence or distant disease. Given these findings, the authors concluded that the cytokeratin-positive cells in the axillary lymph nodes of 6 of 26 patients with DCIS were likely a result of passive transport of cells displaced into lymphatics during previous biopsy and were not clinically significant. They cautioned against overinterpretation of positive lymph nodes detected by immunohistochemistry in DCIS, as they could represent false-positive results, and result in overtreatment of patients.

Our study had some limitations. First, potential limitations are inherent to any single-institutional, retrospective study. Notwithstanding, results of this study can be valuable to other institutions with respect to their own recommendations on the use of SLNB in patients with an initial diagnosis of DCIS. The fact that our group performed this type of analysis opens this subject to critical analysis and debate among other cancer experts and may be useful in the design of prospective trials addressing this issue. Second, the patients in our study had a short followup period.

In conclusion, despite diagnostic uncertainty and inherent sampling error associated with conventional pathologic techniques, we cannot emphasize enough the importance of an extensive and thorough examination of the primary breast tumor to exclude an invasive component and decrease the prevalence of unexpected SLN metastases. The issue of SLNB in patients with an initial diagnosis of DCIS requires further investigation with larger numbers of patients and longer followup times. The clinical and pathologic factors that predict invasive disease need to be confirmed and will ultimately serve as a guide to the selective use of SLNB in these patients. With longer followup, we will be able to determine the significance of a positive SLN in patients with DCIS and address the need for adjuvant therapies. We consider that immunohistochemical evaluation of SLNs is still investigational. From our study, we believe that SLNB should not be performed routinely in all patients with an initial diagnosis of DCIS. The option of performing SLNB in patients with an initial diagnosis of DCIS should be discussed only with patients suspected of having underlying invasive disease, including patients who

are younger, are diagnosed by core-needle biopsy, or have large ( $\geq 4$  cm) or high-grade DCIS. The discussion of the risks and benefits of SLNB is especially important in patients scheduled to undergo mastectomy, as these patients could be potentially spared an ALND if SLNB were performed at the time of mastectomy.

#### Author Contributions

Study conception and design: Yen, Kuerer

Acquisition of data: Yen

Analysis and interpretation of data: Yen, Hunt, Ross, Mirza, Kuerer

Drafting of manuscript: Yen

Critical revision: Hunt, Babiera, Meric-Bernstam, Singletary, Symmans, Giordano, Feig, Ames

Statistical expertise: Mirza

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