RESEARCH ARTICLE

Factors Predicting Microinvasion in Ductal Carcinoma *in situ*

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Abstract

Background: Whether sentinel lymph node biopsy (SLNB) should be performed in patients with pure ductal carcinoma in situ (DCIS) of the breast has been a question of debate over the last decade. The aim of this study was to identify factors associated with microinvasive disease and determine the criteria for performing SLNB in patients with DCIS. Materials and Methods: 125 patients with DCIS who underwent surgery between January 2000 and December 2008 were reviewed to identify factors associated with DCIS and DCIS with microinvasion (DCISM). Results: 88 patients (70.4%) had pure DCIS and 37 (29.6%) had DCISM. Among 33 DCIS patients who underwent SLNB, one patient (3.3%) was found to have isolated tumor cells in her biopsy, whereas 1 of 14 (37.8%) patients with DCISM had micrometastasis (7.1%). Similarly, of 16 patients (18.2%) with pure DCIS and axillary lymph node dissection (ALND) without SLNB, none had lymph node metastasis. Furthermore, of 20 patients with DCISM and ALND, only one (5%) had metastasis. In multivariate analysis, the presence of comedo necrosis [relative risk (RR)=4.1, 95% confidence interval (CI)=1.6-10.6, P=0.004], and hormone receptor (ER or PR) negativity (RR=4.0, 95%CI=1.5-11, P=0.007), were found to be significantly associated with microinvasion. Conclusions: Our findings suggest patients presenting with a preoperative diagnosis of DCIS associated with comedo necrosis or hormone receptor negativity are more likely to have a microinvasive component in definitive pathology following surgery, and should be considered for SLNB procedure along with patients who will undergo mastectomy due to DCIS.

Keywords: Ductal carcinoma *in situ* - sentinel lymph node biopsy - microinvasion

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Introduction

Ductal carcinoma *in situ* (DCIS) of the breast is a noninvasive or preinvasive lesion characterized by malignant ductal cells confined to the duct lumen, without evidence of invasion into the adjacent breast stroma. Twenty years ago, DCIS was an uncommon diagnosis, accounting for only 3-5% of breast cancers. However, with the introduction of screening mammography, this figure has more recently increased to 20-25% (Rosner et al., 1980; Greenlee et al., 2001). By definition, DCIS is not a fatal disease. Nevertheless, it is known that some women treated for DCIS subsequently develop invasive breast cancer, which is associated with a poorer prognosis. Moreover, in rare cases, DCIS may behave as an aggressive breast cancer, whereby a woman may die from metastatic disease without any evidence of invasive cancer at the time of being treated for DCIS (Altintas et al., 2009).

The management of the axilla in DCIS patients has also changed dramatically in recent years. Because DCIS is preinvasive and does not have the potential to spread to regional lymph nodes, axillary dissection for DCIS, which was commonly practiced in the 1980s, was gradually abandoned during the 1990s. Subsequent follow-up analysis revealed that the omission of axillary dissection in patients with pure *in situ* disease had no adverse effect on patient survival or disease recurrence (Baxter et al., 2004; Mabry et al., 2006).

The rate of SLNB positivity has been found to range from 9.6% to 14% in patients with DCIS with microinvasion (DCISM) (Wilkie et al., 2005; Katz et al., 2006; Intra et al., 2008). Therefore, the use of SLNB is sufficiently more justified in patients with DCISM, as well as in patients with invasive breast cancer. However, there continues to be an ongoing debate about whether SLNB is appropriate for patients with pure DCIS for routine use of sentinel lymph node (SLN) mapping. Many surgeons suggest that SLNB should be used for patients with DCIS who undergo mastectomy, due to the fear that invasive disease will be identified in the final pathology, and subsequent axillary lymph node dissection (ALND) will be required. Furthermore, many surgeons still believe that a subset of patients who are at high risk for microinvasive disease and subsequent axillary metastasis may benefit from SLNB. This emphasizes the importance

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of identifying factors that can further subtype DCIS in order to characterize the potential for microinvasion, which affects treatment and surgical procedures.

The aims of this study were to examine the clinical and pathologic characteristics of patients with DCIS or DCISM, distinguishing *in situ* disease from microinvasive disease, and to determine the feasibility of performing SLNB in these patients.

Materials and Methods

Patients

Between January 2000 and December 2008, a total of 1839 patients with a diagnosis of breast cancer underwent surgery at our Breast Unit of the General Surgery Department. Among these patients, we identified 125 patients with a final diagnosis of DCIS or DCISM (6.8%) that were included into this retrospective study. All of the data on patient and tumor characteristics were retrieved from the patients' charts and the following information was recorded for analysis: patient age at diagnosis, nuclear grade, histological pattern, presence or absence of comedonecrosis, size of lesion, and the presence or absence of disease at the margins. The follow-up time along with the information on disease recurrence, presence of metastasis, patient death, and cause of death were also recorded.

Histopathology

The distance of the tumor to the inked edge of the specimen was reported for every marking margin and was measured using a micrometer. The distance used to define the margin width was the narrowest distance between the tumor and any inked margin. Negative margins were defined as those with a width of at least 2 mm. Microinvasion was defined as a microscopic focus of invasive cancer cells extending beyond the basement membrane into the adjacent tissue, with no focus greater than 0.1 cm in dimension, according to the guidelines of the American Joint Committee on Cancer (AJCC) 2002 (Edge et al., 2009). Immunostaining for estrogen receptor (ER) and progesteron receptor (PR) was performed on full tissue sections, and cases with 1% or more positive staining were considered as positive staining. HER2 positivity was defined as those cases where IHC staining was 3+ alone or 2+ with fluorescence *in situ* hybridization (FISH)-positivity.

SLNBs were harvested using blue dye and/or the lymphosintigraphy technique. Briefly, after the gross measurements were taken, the SLNs of the major axis greater than 0.5 cm were bisected into two pieces, whereas nodes smaller than 0.5 cm were fixed and embedded uncut. The SLNs sent for immediate frozen-section examination and imprint cytologic examination were bisected, and one half was frozen and cut into sections. After frozen sectioning was performed, both halves of the SLNs were fixed and embedded in paraffin. At least four sections were obtained from each block of SLN at different levels (100-500 m apart), and were stained with H&E. When cells in paraffin embedded sections were found to be suspicious by H&E staining, IHC was performed using cytokeratin antibodies. The SLNs were classified as negative or positive, as defined by the seventh edition of the AJCC 2009 staging system (Edge et al., 2009).

Local recurrence was defined as in-breast recurrence after breast conservation, chest wall recurrence after

Table 2. Univariate Analyses for Factors Associated with the Presence of Microinvasion in Ductal Carcinoma *in situ*

Factor	DCIS, (n=88) N (%)	DCISM, (n=37) N (%)	p value
≥50 (vs<50)	47 (53.4)	23 (62.2)	0.434
Tumor palpability+(vs tumor palpability -)	15(17.0)	10(27.0)	0.226
Tumor size >15 mm (vs≤15 mm)	50(56.8)	30(81.1)	0.011
Comedonecrosis+(vs comedonecrosis -)	27(30.7)	23(62.2)	1.001
High nuclear grade (vs other)	34(38.6)	25(67.6)	0.012
ER+(vs ER-)	48(78.7;n=61)	14(43.8;n=32)	0.001
PR+(vs PR-)	41(66.1;n=62)	14(48.3;n=29)	0.105
ER+or PR+(vs other)	50(80.6;n=62)	17(53.1n=32)	0.008
HER2-neu+(vs other)	3(18.8;n=16)	9(39.1;n=23)	0.291
Luminal A (=ER+and/or PR+HER2-) (vs other)	12(80;n=15)	10(50;n=20)	0.089
Luminal B (=ER+ and/or PR+, HER2+) (vs other)	1(6.0;n=15)	1(5;n=20)	0.099
HER2-neu (ER- and/or PR-, HER2-neu+) (vs other)	2(13.3;n=15)	8 (25; n=20)	0.672
Triple negative (=ER-, PR-, HER2-) (vs other)	0(0;n=15)	4(20;n=20)	0.119

*DCIS=ductal carcinoma *in situ*; DCISM=ductal carcinoma *in situ* with microinvasion; ER=estrogen receptor; FISH=fluorescence *in situ* hybridization; IHC=immunohistochemistry; PR=progesteron receptor. "-" and "+" symbols represent negative and positive, respectively

Table 1. Clinicopathological Characteristics of Patients with Ductal Carcinoma *in situ* or Ductal Carcinoma *in situ* with Microinvasion

		Total patient, (n=125) N (%)	DCIS patient, (n=88) N (%)	DCISM patient, (n=37) N (%)	p value
Median (range) follow-up period, in months		53 (12-144)	54 (12-144)	52 (12-132)	0.932
Median (range) age, in years		51 (22-77)	50 (29-77)	51 (22-75)	0.434
Menopausal status	Premenopausal	49 (39.2)	35 (39.8)	14 (37.8)	0.927
	Postmenopausal	76 (60.8)	53 (60.2)	23 (62.2)	
Family history	Positive	25 (20)	17 (19.3)	8 (21.7)	0.809
	Negative	17 (19.3)	71 (80.7)	29 (78.3)	
Tumor size					0.011
Presence of nipple discharge		6 (4.8)	5 (5.7)	1 (2.7)	0.477
Pleomorphic microcalcifications in mammography		82 (65.6)	57 (64.8)	25 (67.6)	0.838
Mass in mammography		27 (21.6)	21 (23.9)	6 (16.2)	0.477

*DCIS=ductal carcinoma *in situ*; DCISM=ductal carcinoma *in situ* with microinvasion

mastectomy, or recurrence within the axilla. All sistemic recurrences (e.g., those in bone, lung, brain) were considered as distant metastases.

Statistical analyses

The Statistical Package for the Social Sciences program, version 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Mann-Whitney U-test, Fisher's exact test and chi-square test were used for analyses where appropriate. The significant factors that were found in univariate analyses were further analyzed by forward logistic regression analysis to identify the independent factors associated with DCIS with microinvasion. A p value less than 0.05 was considered significant.

Results

The clinicopathological characteristics of the DCIS and DCISM patients are compared in Table 1. Among the 125 patients in this study, 88 (70.4%) had pure DCIS, whereas the remaining 37 patients (29.6%) had DCIS associated with microinvasion (DCISM). The median age was 51 years (range, 22-77). Factors including age, or menopausal status, or presence of nipple discharge, presence of pleomorphic microcalcification or a palpable mass were not found to be associated with the presence of microinvasion (Table 1). However, patients with DCISM were more likely to have tumors >15 mm, or with comedo-type necrosis, or with high nuclear grade or with ER negativity or hormone receptor negativity (ER & PR negative) than patients with DCIS (Table 2). Although patients with DCIS were more likely to have luminal A type (ER or PR- positive/HER2-negative) tumors or less likely HER2-neu or pure HER2-neu tumors or triple negative tumors than patients with DCISM, these differences between 2 patient groups did not reach statistical significance (Table 2). In multivariate analysis, presence of comedonecrosis, or hormone receptor negativity (ER/PR-negative) were significantly associated with microinvasion (Table 3).

For preoperative diagnosis, fine needle aspiration was carried out for 4 patients (3.2%), whereas a core biopsy was performed for 9 patients (7.2%), and a vacuum-aspirated biopsy was performed for 4 patients (3.2%). All other patients (n=108, 86.7%) underwent excisional biopsy for histopathological diagnosis. Of them, 80 patients had wire-guided biopsies for nonpalpable lesions. Intraoperative frozen sectioning was performed for 22 patients (17.6%).

Of 125 patients, 74 (59.2%) underwent a mastectomy due to extensive disease. Among the remaining patients, 38 patients were treated with breast conservative surgery (BCS) and radiation therapy (RT), and 13 patients were treated with BCS without RT. Furthermore, any axillary surgery was performed in 83 of the 125 patients during the study period (Table 4).

Of patients with pure DCIS (n=33) who underwent SLNB, 1 patient (3.3%) was found to have isolated tumor cells in SLNB, whereas 1 of 14 patients with DCISM had micrometasis in SLNB (7.1%). Similarly, 16 patients (18.2%) with pure DCIS underwent ALND without SLNB, and none of them were found to have lymph node metastasis. Furthermore, of 20 patients with DCISM who underwent ALND without SLNB, only 1 patient (5%) was found to have lymph node metastasis.

Surgical procedures performed either between 1996 and 2003 or between 2004 and 2008 were compared since routine use of SLNB were started after 2003 (Table 5). We found that the rate of ALND was decreased from 39% between 1996 and 2003 to 15% between 2004 and 2008, and the mastectomy rate was declined from 72% to 43% (p=0.012 and p=0.002, respectively). Contrarily, the SLNB rate was increased from 16% to 59%, and the BCS rates were increased from 28% to 57% (p=0.001 and p=0.008, respectively).

The median follow-up period was 53 months (range, 12-144). Among the patients with BCS, ipsilateral breast cancer recurrence (IBCR) was detected in 3 patients. The IBCR rate was 7.7% for patients with BCS alone and 5.3% for patients with BCS and RT. Of 3 patients with IBCR, 1 patient with a tumor of <15 mm, intermediate grade, and negative clear margins (>1 cm) did not have RT, whereas the other 2 patients had RT, but their surgical margins were found to be close (<1 mm). Interestingly,

Table 3. Multivariate Analysis for Significant Factors Associated with the Presence of Microinvasion in Univariate Analysis*

	Odds ratio (95%CI)	p
Factors associated with the presence of DCISM		
Comedo necrosis (+)	4.1 (1.6-10.6)	0.004
Hormone (ER and/or PR receptor) receptor negativity		
	4.0 (1.5-11)	0.007

*Factors including "tumor size >15 mm", presence of comedo necrosis, high nuclear grade, hormone receptor positivity were further analyzed in forward logistic regression analysis; **CI=confidence interval; DCISM=ductal carcinoma *in situ* with microinvasion

Table 4. Surgical Procedures Performed in Patients with Ductal Carcinoma *in situ* or Ductal Carcinoma *in situ* with Microinvasion

Factor	DCIS (n=88) N (%)	DCISM (n=37) N (%)	Total patients (n=125) N (%)
Mastectomy	51(58.0)	23(62.2)	74(59.2)
Breast conserving surgery	37(42.0)	14(37.8)	51(40.8)
Axillary surgery	49(55.7)	34(91.8)	83(66.4)
SLNB	33(37.5)	14(37.8)	47(37.6)
ALND without SLNB	16(18.2)	20(54.1)	40(32.0)

*ALND=axillary lymph node dissection; CI=confidence interval; DCIS=ductal carcinoma *in situ*; DCISM=ductal carcinoma *in situ* with microinvasion; SLNB=sentinel lymph node biopsy

Table 5. Surgical Procedures Performed among Patients with Ductal Carcinoma *in situ* or Ductal Carcinoma *in situ* with Microinvasion between 1996-2003 and 2004-2008

Surgery	1996-2003 (n=71) N (%)	2004-2008 (n=54) N (%)	p value
Mastectomy	51(72)	23(43)	0.002
Breast conserving surgery	20(28)	31(57)	0.008
Sentinel lymph node biopsy	11(16)	32(59)	<0.001
Axillary lymph node dissection	28(39)	8(15)	0.012

one patient with DCIS who underwent mastectomy due to a 4 cm high-grade tumor had locoregional recurrence in the thoracic wall; therefore the locoregional recurrence rate was 1.4% in patients with a mastectomy. Furthermore, one patient with DCIS who underwent BCS with RT developed distant metastasis in the liver without having any evidence of recurrence in the breast. The median time to any recurrence (local or systemic) was 84 months (range, 40-144).

Discussion

In a previous population-based study, only 1.9% of patients with DCIS died of breast cancer within 10 years of their diagnosis (Greenlee et al., 2001). Despite the relatively benign nature of DCIS, patients have commonly undergone aggressive treatment, similar to that recommended for patients with invasive breast cancer (Skinner et al., 2001). The risks of overdiagnosis and overtreatment of DCIS patients have been recognized (Greenlee et al., 2001; Adlard et al., 2006). Nonetheless, this issue has been in debate as some cases of DCIS have a less benign course than other cases; some histologic features, particularly the presence of comedo histology, are associated with a more aggressive disease behavior (Baxter et al., 2004).

Variations in the treatment of patients with DCIS have been described previously (Baxter et al., 2004; Katz et al., 2006). Ernster et al. (1996) found that the proportion of patients with DCIS who were treated with mastectomy decreased from 71% in 1983 to 44% in 1992 (Ernster et al., 1996). The authors also noted that 44% of the patients in 1992 who underwent lumpectomy received RT. Furthermore, Winchester et al. (1995) evaluated the treatment of DCIS patients between 1985 and 1993 using the National Cancer Database, and they found a statistically significant increase in the use of BCS (Winchester et al., 1995). In contrast, they also noted that the rate of RT after lumpectomy increased from 38% to 54% over the study period. Furthermore, up to half of the DCIS patients reportedly underwent ALND, a potentially morbid procedure with questionable long-term benefits and a limited role in routine treatment of this disease (Lagios et al., 1989; Sakr et al., 2006; Zavagno et al., 2007). Similarly, according to a study by Baxter et al. (2004), the rate of mastectomy decreased from 43% in 1992 to 28% in 1999, and the rate of ALND decreased from 34 to 15% during the same time period (Baxter et al., 2004). In agreement with all these studies, we also found an increased rate of BCS and SLNB in patients with DCIS or DCISM at our institution after 2004, whereas the mastectomy rate and ALND rate were significantly decreased between 2004 and 2008 compared to the corresponding rates for the period between 1996-2004 (Ozmen et al., 2006).

The significance of DCISM is still debated and clinical management of this condition remains controversial (Silver et al., 1998; Zavagno et al., 2007). DCISM accounts for less than 1% of all breast cancers, and 13.5% of all DCIS cases have a microinvasive component (Siverstein et al., 1990). There has been a lack of agreement in the literature as to whether DCISM should be considered and treated simply as a stage 0 DCIS lesion (Cavaliere et al., 2006), or instead as a small invasive cancer (Intra et al., 2003). According to various studies, the rate of imaging appearance of DCISM lesions as masses with or without associated calcifications on mammography range between 17% and 57% (Vieira et al., 2010). However, this imaging feature is less commonly encountered in cases with pure DCIS, where calcifications in the absence of a mass are a more common finding (Dershaw et al., 1989; Ikeda et al., 1989). The mammographic microcalcification rate in patients with DCISM ranges between 61% and 83% (Sakr et al., 2006; Zavagno et al., 2007). In our study, the majority of patients with DCISM (68%) had microcalcifications, whereas only 16% of them had a mammographic mass. Among the patients with DCIS, 65% had microcalcification and 24% had a mammographic mass lesion. Therefore, there was no significant difference in the rates of mammographic microcalcifications or mass lesions between the DCIS and DCISM patients in our series.

The advent of SLNB and its low morbidity prompted interest in its use in patients with DCIS who were considered to be at high risk of harboring an invasive component, such as those patients with adverse clinical or histological features (palpable tumor, mammographic mass, high nuclear grade). SLNB has been generally recommended as an initial surgery to prevent the necessity of a secondary surgery, or when mastectomy is indicated, because a secondary SLNB is not feasible after mastectomy. Routine use of SLNB in DCIS patients is controversial. Although some authors recommend that an SLNB should be performed in all patients with a preoperative core biopsy diagnosis of DCIS, (Anderson et al., 2000; Silverstein et al., 2001) it should be noted that Intra et al. reported a low incidence of SLN involvement (1.4%) in 854 patients with pure DCIS (Intra et al., 2008). In concordance with such previous studies, we also found a low rate of SLN involvement (3.3%) in patients with pure DCIS, and a relatively higher incidence of lymph node involvement (7%) in patients with DCISM. Some previous studies have investigated predictors of an invasive component in DCIS to select the most appropriate candidates to undergo SLNB (Lagios et al., 1989; Yen et al., 2005; Tan et al., 2007).

The incidence of microinvasion in DCIS varies according to the size and extent of the index lesion. Lagios et al. reported a 2% incidence of microinvasion in patients with DCIS, measuring less than 25 mm in diameter, compared with a 29% incidence of microinvasion in index lesions larger than 26 mm (Lagios et al., 1989). Histopathologically, these lesions tended to be high-grade lesions of various histologic subtypes, most with comedonecrosis, palpable masses, and nipple discharge. Tan et al. (2007) found that the presence of comedonecrosis and a diagnosis of an invasive component by core-needle biopsy were independent risk factors for invasion in patients undergoing mastectomy and SLNB for DCIS; however, these authors found no risk factors that were predictive of SLN metastases (Tan et al., 2007).

Similarly, Yen et al. (2005) revealed 4 independent

predictors of invasive cancer: a patient age of 55 years or younger; a diagnosis by core-needle biopsy; a mammographic DCIS size of at least 4 cm; and high-grade DCIS (Yen et al., 2005). In agreement with all these previous studies, the patients with DCISM included in our present study were more likely to have a tumor size >15 mm, or a tumor with comedonecrosis, or with a high nuclear grade, or with hormone receptor (ER/PR-negative) negativity.

Studies showed that ER and PR expression range from 60 to 78% in DCIS (Daly et al., 2006). Similarly, 81% of tumors with pure DCIS were found to express estrogen or progesterone receptors in our study. In concordance with the findings of two recent reports (Park et al., 2010; Yu et al., 2011), the patients with DCIS in our study were significantly more likely to have luminal A type (ER+ or PR+/HER2-neu-negative) tumors than patients with DCISM, but this comparison did not reach statistical significance due to the limited number of IHC-stained tumor samples available.

HER2-neu is one of the epidermal growth factor receptor (EGFR) family, accelerating cell proliferation, and enhancing malignant behavior. HER2-neu overexpression was found with breast cancer invasion and poor prognosis. There are controversial findings regarding HER2-neu overexpression in DCIS in regards to invasive breast cancer. Our findings have shown a trend for an increased rate of HER2-neu overexpression in patients with DCISM in comparison to patients with pure DCIS which was not statistically significant due the small sample size. Some previous studies interestingly found HER2-neu overexpression was lower in invasive breast cancer than pure DCIS, whereas tumors with DCIS and DCISM showed similar rates of HER2-neu overexpression (Wei et al., 2012). However, Roses et al. (2009) demonstrated that although high nuclear grade, large lesion size, and HER2 overexpression were all associated with the presence of invasive disease on univariate analysis, HER2 was the only significant predictor for the presence of invasive disease after multivariate adjustment (odds ratio, 6.4; P=0.01) (Roses et al., 2009). Therefore, they strongly suggest that HER2 overexpression in DCIS lesions predicts the presence of invasive foci in patients with DCIS indicating that HER2 expression may reflect an important pathway through which DCIS lesions may progress toward invasion.

Furthermore, triple negative breast cancer has infrequently been seen in both pure DCIS or DCISM (Table 2) in concordance with some recent reports (Park et al., 2010; Yu et al., 2011). Therefore, determining the criteria associated with invasive disease seems the most important strategy in the management of patients with a preoperative diagnosis of DCIS to determine whether a SLNB should be performed.

Silverstein (2003) noted that DCIS is a heterogeneous group of lesions, and thus a uniform treatment policy is inappropriate, as different patients will require or benefit from different treatment options (Silverstein, 2003). In a review of 21 studies involving DCIS patients who were treated by mastectomy, a 0.4% incidence of recurrence was observed (Lagios et al., 1989; Boyages et al., 1999; Silverstein et al., 1999; Mirza et al., 2000). Significantly lower local recurrence rates after a total mastectomy compared to corresponding rates after BCS were confirmed by Cutuli et al. (2001), who reported local recurrence rates of 2.1%, 30.1%, and 13.8% in the mastectomy, BCS alone, and BCS with RT patient groups, respectively, after a 91 month follow-up period (Cutuli et al., 2001). Randomized trials also confirmed this trend and revealed the benefit of RT and hormonal treatment after BCS to reduce the rate of IBCR (Fisher et al., 1998; Houghton et al., 2003). In our study, at a median follow-up of 53 months, the IBCR rate was 7.7% for patients with BCS alone and 5.3% for patients with BCS and all the patients who had an IBCR after BCS with RT had close surgical margins (<1 mm), suggesting wide surgical margins seem to be important in local control of DCIS. However, the locoregional recurrence rate in patients with mastectomy was quite low (1.4%), and was similar to those rates in previous reports. Our study has however some limitations regarding the number of patients included into the study, and thus other clinical and pathologic characteristics may also be important in predicting the risk of recurrent disease in these patients.

In conclusion, our results suggest that patients with comedo-type necrosis or negative hormone receptors were more likely to have microinvasive disease than other DCIS patients. Furthermore, our findings indicate that SLNB should be performed in patients with DCIS associated with microinvasion, and in patients who have predictive characteristics for microinvasive disease and/or in whom mastectomy was planned as the definitive breast surgery.

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