

# Sentinel lymph node biopsy in patients with breast ductal carcinoma *in situ*: Chinese experiences

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**Abstract.** The axillary treatment of patients with ductal carcinoma *in situ* (DCIS) remains controversial. The aim of the present study was to evaluate the roles of sentinel lymph node biopsy (SLNB) in patients with breast DCIS. A database containing the data from 262 patients diagnosed with breast DCIS and 100 patients diagnosed with DCIS with microinvasion (DCISM) who received SLNB between January 2002 and July 2014 was retrospectively analyzed. Of the 262 patients with DCIS, 9 presented with SLN metastases (3 macrometastases and 6 micrometastases). Patients with large tumors diagnosed by ultrasound or with tumors of high histological grade had a higher positive rate of SLNs than those without ( $P=0.037$  and  $P<0.0001$ , respectively). Of the 100 patients with DCISM, 11 presented with metastases. Younger patients had a higher positive rate of SLNs ( $P=0.028$ ). According to the results of this study and the systematic review of recent studies, the indications of SLNB for patients with DCIS are as follows: SLNB should be performed in all DCISM patients and in those DCIS patients who received mastectomy, and could be avoided in those who received breast-conserving surgery. However, SLNB should be recommended to patients who have high risks of harboring invasive components. The risk factors include a large, palpable tumor, a mammographic mass or a high histological grade.

## Introduction

With improvements to the breast cancer screening program, more and more women with early breast cancer are being diagnosed and treated. In early invasive breast cancer patients, sentinel lymph node biopsy (SLNB) has become a routine procedure, as it provides accurate axillary staging, while sparing node-negative patients the morbidity associated with axillary lymph node dissection (ALND) (1). At present, SLNB is the standard treatment for patients with clinical node-negative invasive carcinoma, with the exception of those patients with T4d stage disease (2). However, the axillary treatment of patients with ductal carcinoma *in situ* (DCIS) remains controversial (3). These patients, who exhibit pre-invasive tumors with no invasive component, are theoretically believed to have no chance of lymph node metastases. However, certain patients with DCIS may harbor an unrecognized focus of invasion in the tumor and therefore have lymph node metastases.

China Breast Cancer Clinical Study Group-001 is a prospective multi-center clinical trial conducted to study the feasibility of using SLNB as a substitute for ALND in 3466 Chinese breast cancer patients recruited from 13 institutes between January 2002 and July 2014. The primary objectives were determining the disease-free survival and complications of SLNB and ALND. The secondary objectives included overall survival, SLN intraoperative diagnosis, micrometastasis detection and prognosis, and radiological safety of the two techniques. All patients enrolled in the study were  $\geq 18$  years of age with a diagnosis of early breast cancer and scheduled for a SLNB. Patients who had undergone previous ipsilateral axillary surgery were excluded from the study (4).

The present study selected 362 patients with DCIS or DCIS with microinvasion (DCISM; with the largest diameter of the invasive component of  $<1$  mm) from the CBCSG001 database and analyzed the frequency and the risk of SLN metastases in these patients.

## Materials and methods

**Patients.** Of 362 patients selected from the database, 262 patients presented with the final pathology of DCIS and 100 with DCISM. All patients were  $\geq 18$  years of age (range, 22-80 years;

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Table I. Positive rate of SLNs in patients with ductal carcinoma *in situ*.

Characteristic	SLN-positive	SLN-negative	P-value
Mean age, years <sup>a</sup>	46±7	48±11	0.648
Tumor size on ultrasound, cm	2.93±0.87	1.95±1.40	0.037
Clinical palpable mass, n			0.407
Yes	9	235	
No	0	18	
Location, n			0.420
Upper outer quadrant	8	154	
Upper inner quadrant	0	32	
Lower outer quadrant	1	22	
Lower inner quadrant	0	21	
Central area	0	24	
Breast surgery, n			0.535
Breast-conserving treatment	7	172	
Mastectomy	2	81	
ER status, n			0.246
Positive	5	185	
Negative	4	68	
HER-2 status, n			0.402
Positive	4	79	
Negative	5	174	
Histopathological grade, n			<0.0001
High	8	119	
Medium	1	94	
Low	0	40	

SLN, sentinel lymph node; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2.

median, 47 years) and scheduled for a SLNB. The study was approved by the Ethics Committee of the Shandong Cancer Hospital and informed consent was obtained from each patient. Patients who had undergone previous ipsilateral axillary surgery were excluded from this study.

**Identification of SLNs.** Sulfur colloid (SC) was labeled with Technetium-99m (<sup>99m</sup>Tc) subsequent to filtration through a millipore filter with a 220-nm pore size. <sup>99m</sup>Tc-SC ranging from 7.2-37.0 MBq, in 0.5-2.0 ml, was injected subcutaneously above the primary tumor on the day prior to surgery or at least 4 h prior to surgery on the actual day. SLNs were identified by combining the use of an intraoperative  $\gamma$ -detector (Neo2000 Gamma Detection System; Johnson and Johnson, New Brunswick, NJ, USA) and blue dye. Methylthionium (1%; 4ml) was injected subcutaneously above the primary tumor or around the biopsy cavity 10 min prior to surgery. Lymph nodes with blue lymphatic vessels directly leading to them (SLNs by blue dye) and those with a radioactivity count higher than 10% of the highest radioactivity count of the lymph node (SLNs by isotope) were regarded as SLNs.

**Evaluation of primary tumors.** The excised breast lesions were sampled with serial sections, with at least one block

per centimeter. In selected cases, secondary breast tissue sections were obtained. The search for microinvasive foci was performed with HE serial sections and immunostaining for smooth muscle actin and cluster of differentiation 10 for the detection of myoepithelial cells. The largest diameter of the invasive component of the DCISM was <1 mm.

**Evaluation of SLNs.** The SLNs were identified and dissected, and then they were sectioned along the long axis into two blocks. Intraoperatively, all blocks were assessed by frozen section and touch imprint cytology. ALND was only performed if any of the intraoperative tests were positive.

Post-operatively, all node blocks were fixed in 10% buffered formalin and paraffin embedded, and one 4-6- $\mu$ m thick slide was taken from each block. Metastases were classified according to the 6th criterion of the American Joint Cancer Committee (5). Macrometastases ( $\geq 2$  mm), micrometastases (0.2-2 mm) and isolated tumor cells ( $\leq 0.2$  mm) were all considered node-positive.

**Statistical analysis.** The primary analysis was performed to determine the frequency of SLN metastases in patients with post-operative diagnoses of DCIS and DCISM.  $\chi^2$  tests or Fisher's exact tests were performed to compare the rate

Table II. Positive rate of SLNs in patients with ductal carcinoma *in situ* with microinvasion.

Characteristic	SLN positive	SLN negative	P-value
Mean age, years	41±8	48±10	0.028
Tumor size by ultrasound, cm	2.18±1.03	2.00±1.17	0.799
Location			0.773
Upper outer quadrant	6	50	
Upper inner quadrant	2	18	
Lower outer quadrant	1	6	
Lower inner quadrant	0	7	
Central area	2	8	
Breast surgery			0.687
Breast-conserving treatment	9	68	
Mastectomy	2	21	
ER status			0.479
Positive	8	55	
Negative	3	34	
HER-2 status			0.459
Positive	1	16	
Negative	10	73	

SLN, sentinel lymph node; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2.

between different groups. Statistical analyses were performed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA) and  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

A total of 1,145 SLNs were removed (mean, 3.16) from 362 patients. Of the 362 patients, 20 (5.52%) exhibited metastases.

Of the 262 patients with DCIS, 9 (3.4%) presented with SLN metastases (3 macrometastases and 6 micrometastases). All 9 patients received ALND and only 1 patient with SLN macrometastases exhibited non-sentinel axillary lymph node (nSLN) metastases. As shown in Table I, the positive rate of SLNs was not associated with patient age, primary tumor location, whether the mass was palpable, breast surgery type, or estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER-2) status. However, patients with large tumors diagnosed by ultrasound or with tumors of high histological grade had a higher positive rate of SLNs than those without ( $P = 0.037$  and  $P < 0.0001$ , respectively).

Of the 100 patients with DCISM, 11 presented with metastases. Of these, 4 patients exhibited SLN macrometastases, six exhibited micrometastases and 1 possessed isolated tumor cells. Following ALND, 3 patients with SLN macrometastases and 2 patients with SLN micrometastases were diagnosed with nSLN metastases. The positive rate of SLNs was not associated with tumor size, primary tumor location, breast surgery type, or ER and HER-2 status. However, younger patients had a higher positive rate of SLNs ( $P = 0.028$ ) (Table II).

## Discussion

Theoretically, DCIS without any invasive component cannot invade the lymphatic system and the cancer cells cannot spread to the lymph nodes. Thus, axillary staging appears to be an overtreatment in these patients. However, the fact is that a fraction of patients with the final pathology of DCIS has lymph node metastases. Doubt arises with regard to whether the condition is really pure DCIS. Due to sampling error in the final pathology, DCIS may be upstaged to DCISM or invasive cancer after a more thorough evaluation of the tumor. The interval of pathological serial sections determines the inevitability of this error (6).

To date there has been no prospective randomized trial to address the value of SLNB in patients with DCIS. In the present study, the PubMed database was searched between January 2000 and the current date (July 2014), and the positive rates of SLNs in patients with a final pathology of DCIS in other international studies are listed in Table III (6-22). There are large differences among these studies. We believe that the reason for this lies in the different number of patients enrolled and the different criteria of sampling method. The present study shows that the positive rate of SLNs in patients with the final pathological diagnosis of DCIS was 3.4%, and the positive rate of SLNs in patients with DCISM was significantly higher than that of DCIS ( $P = 0.005$ ). The study also indicated that patients with large tumors diagnosed by ultrasound or with tumors of high histological grade have a relatively higher positive rate of SLNs than those without.

The pre-operative minimally invasive biopsy also has its limitations, such as the sampling error. A substantial fraction of women identified with DCIS on a core needle

Table III. Positive rate of sentinel lymph nodes in patients with the final pathology of ductal carcinoma *in situ*.

First author (ref.)	Year	Sample size, n	Positive rate, n (%)
Cserni (6)	2002	10	1 (10.0)
Kelly <i>et al</i> (7)	2003	131	3 (2.3)
Intra <i>et al</i> (8)	2003	223	7 (3.1)
Farkas <i>et al</i> (9)	2004	44	0 (0.0)
Veronesi <i>et al</i> (10)	2005	508	9 (1.8)
Zavagno <i>et al</i> (11)	2005	102	2 (2.0)
Katz <i>et al</i> (12)	2006	110	8 (7.3)
Mabry <i>et al</i> (13)	2006	171	10 (5.8)
Leidenius <i>et al</i> (14)	2006	74	5 (6.8)
Sakr <i>et al</i> (15)	2006	39	4 (10.3)
Di Saverio <i>et al</i> (16)	2007	32	4 (12.5)
Yi <i>et al</i> (17)	2008	475	9 (1.9)
Dominguez <i>et al</i> (18)	2008	158	16 (10.1)
Tada <i>et al</i> (19)	2010	255	1 (0.4)
Miyake <i>et al</i> (20)	2011	66	0 (0.0)
Ozkan-Gurdal <i>et al</i> (21)	2014	33	1 (3.0)
Zetterlund <i>et al</i> (22)	2014	753	11 (1.5)

Table IV. Positive rate of sentinel lymph nodes in patients with the pre-operative pathology of ductal carcinoma *in situ*.

First author (ref.)	Year	Sampling size, n	Positive rate, n (%)
Klauber-DeMore <i>et al</i> (23)	2000	76	9 (11.8)
Pendas <i>et al</i> (24)	2000	87	5 (5.7)
Wilkie <i>et al</i> (25)	2005	559	27 (4.8)
Mittendorf <i>et al</i> (26)	2005	41	2 (4.9)
Camp <i>et al</i> (27)	2005	43	5 (11.6)
Yen <i>et al</i> (28)	2005	141	12 (8.5)
Takács <i>et al</i> (29)	2006	44	0 (0.0)
Fraile <i>et al</i> (30)	2006	142	10 (7.0)
Moran <i>et al</i> (31)	2007	35	3 (8.6)
Meijnen <i>et al</i> (32)	2007	30	5 (16.7)
Moore <i>et al</i> (33)	2007	470	43 (9.1)
Dominguez <i>et al</i> (18)	2008	177	20 (11.3)
Sakr <i>et al</i> (34)	2008	110	6 (5.5)
van la Parra <i>et al</i> (35)	2008	51	5 (9.8)
Yi <i>et al</i> (17)	2008	624	40 (6.4)
Doyle <i>et al</i> (36)	2009	145	7 (4.8)
Schneider <i>et al</i> (37)	2010	110	15 (13.6)
Kurniawan <i>et al</i> (38)	2010	349	65 (18.6)
Miyake <i>et al</i> (20)	2011	103	2 (1.9)
Son <i>et al</i> (39)	2011	66	1 (1.5)
Chin-Lenn <i>et al</i> (40)	2014	306	3 (1.0)
Guillot <i>et al</i> (41)	2014	221	20 (9.0)
Osako <i>et al</i> (42)	2014	336	13 (3.9)

biopsy prove to have an invasive component following the final pathological evaluation. The positive rates of SLNs in patients with the pre-operative pathology of DCIS in the other

studies are listed in Table IV (17,18,20,23-42). The predictors for patients with invasive cancer in this setting are listed in Table V (17,20,25,26,28,31,32,34,36,38-54). Although there

Table V. Predictors of invasive disease in patients with a pre-operative biopsy diagnosis of DCIS.

First author (ref.)	Total patients, n	Patients upstaged to invasive cancer, n (%)	Significant predictors
Yi <i>et al</i> (17)	624	149 (23.9)	Core biopsy; DCIS size, >5 cm
Miyake <i>et al</i> (20)	103	2 (1.9)	Palpable tumor; tumor size, ≥2.0 cm on MRI
Wilkie <i>et al</i> (25)	675	66 (9.8)	High-grade DCIS; mammographic mass; microinvasion
Mittendorf <i>et al</i> (26)	30	6 (20.0)	Diagnosis by core-needle biopsy
Yen <i>et al</i> (28)	398	80 (20.1)	Age, ≤55 years; mammographic size, ≥4 cm; grade 3 DCIS; diagnosis by core-needle biopsy
Moran <i>et al</i> (31)	62	20 (32.3)	DCIS size, >2.5 cm or if mastectomy was required
Meijnen <i>et al</i> (32)	171	45 (26.3)	Palpable lesion; mammographic mass; intermediate/poor grade
Sakr <i>et al</i> (34)	110	31 (28.2)	DCISM; large DCIS
Doyle <i>et al</i> (36)	145	55 (37.9)	Radiological mass; areas of invasion, <1 mm
Kurniawan <i>et al</i> (38)	375	65 (17.3)	Palpable lesions; non-calcified mammographic features (mass, architectural distortion, non-specific density); mammographic size, ≥20 mm; prolonged screening interval, ≥3 years; DCIS grade (univariate analysis)
Son <i>et al</i> (39)	78	14 (17.9)	Large tumor size; HER2 overexpression
Chin-Lenn <i>et al</i> (40)	394	9 (2.3)	Larger pre-operative tumor size
Guillot <i>et al</i> (41)	241	85 (35.3)	Palpable tumor; high-grade DCIS; detection of an opacity by mammography
Osako <i>et al</i> (42)	336	113 (33.6)	Palpability; mammographic mass; and calcifications (spread, >20 mm)
Rutstein <i>et al</i> (43)	254	21 (8.3)	<12 core samples (size, 11-14 gauge); comedo necrosis
Goyal <i>et al</i> (44)	587	220 (37.5)	Clinically palpable mass; mammographic mass
Huo <i>et al</i> (45)	200	41 (20.5)	Mass lesion on imaging; lesion, >1.5 cm; high nuclear grade; presence of lobular cancerization
Hoorntje <i>et al</i> (46)	255	41 (16.1)	Grade 3 DCIS; periductal inflammation in core biopsies; large area of calcification
Renshaw (47)	91	17 (18.7)	Comedo DCIS with cribriform/papillary pattern; DCIS size, >4 mm with lobular extension
Jackman <i>et al</i> (48)	1326	183 (13.8)	Diagnosis by core-needle biopsy; mammographic mass; ≥10 cores per lesion
King <i>et al</i> (49)	140	36 (25.7)	Mass on breast imaging
Lee <i>et al</i> (50)	59	17 (28.8)	Inflammatory infiltrate
Trentin <i>et al</i> (51)	733	148 (20.2)	Mammographic size, >20 mm; residual lesion on post-VABB mammogram; age, <40 years
Lee <i>et al</i> (52)	493	123 (24.9)	Larger DCIS lesion (at least 15 mm); lack of hormone receptor expression; intermediate or high nuclear grade; diagnosis on core biopsy compared with vacuum-assisted biopsy; non-cribriform subtype of DCIS
Park <i>et al</i> (53)	340	145 (42.6)	Palpability; mass or calcification by ultrasonography; grade; suspicious microinvasion; biopsy method (univariate analysis)
Sculz <i>et al</i> (54)	205	37 (18.0)	Palpability; ultrasonographic calcification or mass; suspicious microinvasion; core needle biopsy (multivariate analysis)
			Lesion palpability; mass lesion on ultrasound; presence of a mammographically detectable mass; architectural distortion or density; BI-RADS score of 5, lesion diameter, ≥50 mm; ≥50% of histologically affected ducts (univariate analysis); palpable mass (multivariate analysis)

DCIS, ductal carcinoma *in situ*; DCISM, DCIS with microinvasion; MRI, magnetic resonance imaging; BI-RADS, breast imaging-reporting and data system.

is currently no validated evidence-based medicine model to predict which patients with the pre-operative diagnosis of

DCIS should accept SLNB, patients that are highly suspected to have an invasive component should be advised to undergo



SLNB. The common predictors in these studies include large, palpable tumors, mammographic masses and high histological grade.

The American Society of Clinical Oncology panels have updated the guidelines of SLNB for patients with early-stage breast cancer recently, and the guidelines of SLNB for patients with DCIS has been revised accordingly (3). For women with a core needle biopsy showing DCIS who are being treated with breast-conserving surgery, the guidelines state that there is no evidence to support performing SLNB, and that SLNB may be performed as a separate second procedure in those identified with invasive cancer. The exceptions to this may include cases in which breast imaging or a physical examination identify a clear mass that is characteristic of invasive cancer or a large area of calcification without a mass, where there is a high probability of locating invasive cancer in the resection specimen. Upon performing a mastectomy, the guidelines suggest that SLNB may be warranted due to the possibility of finding an invasive component in the final pathology, and the disruption of the lymphatics by the mastectomy may preclude a subsequent SLNB.

According to the results of the present study and the systematic review of recent studies, the indications of SLNB for patients with DCIS are as follows: SLNB should be performed in all DCIS patients and in those DCIS patients who received mastectomy, and could be avoided in those who received breast-conserving surgery. However, SLNB should be recommended to patients who have high risks of harboring invasive components. The risk factors include large, palpable tumors, mammographic mass and a high histological grade.

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