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PRECLINICAL STUDY

Prognostic impact and possible pathogenesis of lymph node metastasis in ductal carcinoma in situ of the breast

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Abstract

Purpose Ductal carcinoma in situ (DCIS)—preinvasive breast cancer—with lymph node metastasis can clinically be treated as different stages: occult invasive cancer with true metastasis (T1N1) or pure DCIS with iatrogenic dissemination (TisN0). In this retrospective cohort study, we aimed to elucidate the prognostic impact and possible pathogenesis of nodal metastasis in DCIS to improve clinical management.

Methods Subjects were comprised of 427 patients with routine postoperative diagnosis of DCIS who underwent sentinel node (SN) biopsy using molecular whole-lymph-node analysis. Clinicopathological characteristics and prognosis were compared between SN-positive and -negative patients. Primary tumour tissues of SN-positive patients were exhaustively step-sectioned to detect occult invasions, and predictive factors for occult invasion were investigated. Median follow-up time was 73.6 months.

Results Of the 427 patients, 19 (4.4%) were SN-positive and 408 (95.6%) were SN-negative. More SN-positive patients received adjuvant systemic therapy than SN-negative patients (84.2% vs. 5.4%). Seven-year distant disease-free survivals were favourable for both cohorts (SN-positive, 100%; SN-negative, 99.7%). By examining 1421 slides, occult invasion was identified in 9 (47.4%) of the 19 SN-positive patients. Tumour burdens in SN and incidence of non-SN metastasis were similar between patients with and without occult invasion, and no predictive factor for occult invasion was found.

Conclusions Node-positive DCIS has favourable prognosis with adjuvant systemic therapy. Half of the cases may be occult invasive cancer with true metastasis. In practical settings, clinicians may have to treat these tumours as node-positive small invasive cancers because it is difficult to predict the pathogenesis without exhaustive primary tumour sectioning.

Keywords Breast cancer · DCIS · Lymph node metastasis · OSNA · Survival · Parallel progression model

Introduction

Ductal carcinoma in situ (DCIS), the most common type of preinvasive breast cancer, consists of clonal proliferation of cells that appear malignant and that accumulate within the lumen of mammary ducts [1]. By definition, DCIS does not metastasize to the lymph nodes, since the tumour is limited to the epithelial layer and does not reach lymphatic vessels. However, meta-analyses have shown that the incidence of sentinel node (SN) metastases was 3–4% in patients with a final pathological diagnosis of DCIS [2, 3].

The pathogenesis of lymph node metastasis in DCIS and the clinical management of node-positive DCIS remains controversial. Node-positive DCIS can be treated as the following different stages based on the possible pathogenesis: (1) occult invasive cancer with true nodal

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metastasis (pT1mi/1a pN1mi/1a M0: Stage IB or IIA) or (2) pure DCIS with iatrogenic dissemination of tumour or benign epithelial cells into lymph nodes as a result of preoperative breast biopsy (pTis pN0 M0: Stage 0) [4, 5]. According to the current guideline, adjuvant systemic chemotherapy is recommended or considered for Stage IB or IIA tumours for reducing systemic recurrence, while tamoxifen is considered for Stage 0 tumours for reducing in-breast recurrence after breast-conserving surgery [6].

The diagnostic accuracy of both DCIS and lymph node metastasis is dependent on the rigor of the examination. A greater number of small invasive lesions or metastases may be missed if fewer samples of primary tumour or lymph node are examined. Therefore, routine histopathological examinations may underestimate primary tumour and lymph node status due to the partial evaluation of these tissue samples. Regarding the underdiagnosis of primary tumour status, our previous case–control study and another study reported that additional tissue-sectioning examinations revealed occult invasions in 9–58% of patients with a routine postoperative diagnosis of DCIS [4, 7].

For accurate diagnosis of lymph node status, a molecular-based whole-node analysis—one-step nucleic acid amplification (OSNA) assay (Sysmex, Kobe, Japan)—was developed to overcome the limitation of histopathological examinations. The OSNA assay can quantify the total metastatic volume in a whole lymph node based on cytokeratin 19 (CK19) mRNA copy number [8]. Calibration and validation studies have provided reasonable evidence that CK19 mRNA copy numbers detected by the OSNA assay are good estimates of macrometastasis (>2.0 mm in size), micrometastasis (0.2–2 mm), and negative (≤ 0.2 mm), defined by the current cancer staging manual [8, 9]. We have shown that the OSNA whole-node assay detects more cases of metastasis, particularly micrometastasis, than routine histological examinations in both DCIS [5] and invasive breast cancer [10, 11].

Therefore, an exhaustive tissue-sectioning of primary tumours would enable us to detect occult invasions between the specimen surfaces, and the OSNA whole-lymph-node analysis would enable us to more accurately and reproducibly detect clinically relevant small metastases than with histopathological examinations. In this cohort study, in order to elucidate the prognostic impact and possible pathogenesis of nodal metastases in DCIS for improving clinical management of node-positive DCIS, patient characteristics and prognosis were compared between SN-positive and SN-negative DCIS, and the correlation between occult invasion and lymph node status and predictive factors for occult invasion were investigated in SN-positive DCIS.

Patients and methods

Patients

Patients with routine postoperative diagnosis of DCIS who underwent SN biopsy analysed using the OSNA whole-node assay between April 2009 and December 2012 at the Cancer Institute Hospital (Tokyo, Japan) were included in this study. Exclusion criteria were as follows: (1) no SN identified, (2) primary tumour removed by preoperative excisional biopsy, (3) bilateral breast cancer, (4) ipsilateral recurrent breast cancer, and (5) male patient. Pathological T and N classification was classified according the Cancer Staging Manual of the American Joint Committee on Cancer [12].

SN biopsy using the OSNA assay

All patients underwent SN mapping and identification with a radioisotope tracer and/or a blue dye. Radioactive and/or blue lymph nodes were defined as SNs and excised, and whole SNs were evaluated using the OSNA assay without histopathological examination. Between September 2009 and August 2012, the OSNA assay was also used for non-sentinel lymph nodes (non-SNs) in patients who underwent axillary dissection following a metastatic SN biopsy.

In the OSNA assay, whole lymph nodes were homogenized with 4-mL lysis buffer solution (Lynorhag, Sysmex) and centrifuged at 10,000×*g* at room temperature [8]. A total of 2-μL supernatants were analysed with the RD-100i System (Sysmex), an automated molecular detection system that uses a reverse transcription loop-mediated isothermal amplification method and the LynoampBC Kit (Sysmex). The degree of amplification was detected based on the reaction by-product, pyrophosphate. The resultant change in turbidity upon precipitation of magnesium pyrophosphate was then correlated with the CK19 mRNA copy number per microliter of the original lysate via a standard curve established beforehand using three calibrators containing different CK19 mRNA copy numbers. The number of CK19 mRNA copies per μL was extrapolated from the standard curve. The cutoff values for negative/positive and micro-/macrometastasis were set at 250 and 5000 copies/μL, respectively [8].

Routine postoperative diagnosis of DCIS

Partial mastectomy materials were sectioned continuously from the nipple side to the periphery at 5-mm intervals [4, 5, 13]. All sections were histologically examined with haematoxylin and eosin (H&E) staining. Total mastectomy materials were sectioned serially from the nipple to the periphery at 5–7-mm intervals. Sectioning was performed to cover

the entire tumour spread using macroscopic and radiologic findings as references. Most of the sections containing the tumour spread were histologically confirmed with H&E staining.

Comprehensive tissue-sectioning of primary tumours

In order to detect occult invasive lesions in primary tumours of SN-positive patients, all paraffin blocks containing primary tumour were step-sectioned with 500-μm (0.5-mm) intervals until the breast tissue was exhausted [4]. At each level, six microscopic slides were made: one was used for H&E staining and five were stored unstained. All H&E stained slides were microscopically examined. Unstained slides were used for additional immunohistochemical examinations.

Statistical analyses

First, to compare patient characteristics between two groups, the Chi-square test or the Fisher's exact test were performed for categorical variables, and the Mann–Whitney *U* tests were performed for continuous variables. Second, distant disease-free survival (DDFS) and breast cancer-specific survival (BCSS) were used as prognostic endpoints to compare prognosis between two groups. Cumulative survival rates were calculated using the Kaplan–Meier method with censored data, and survival rates between two groups were compared using the log-rank test. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed with the JMP software (version 12.2.0; SAS Institute Japan, Tokyo, Japan).

Results

Patient characteristics between SN-positive and -negative cohorts

Between April 2009 and December 2012, 2725 breast cancer patients underwent SN biopsy using the OSNA whole-node assay, with 566 (20.8%) postoperatively diagnosed with DCIS. Of these 566 patients, 427 were eligible for this study. All patients were Asian women.

Of the 427 patients, 19 (4.4%) were SN-positive and 408 (95.6%) were SN-negative. The tumour characteristics, biopsy methods, and period from breast biopsy to surgery were similar between the SN-positive and SN-negative cohorts (Table 1). Adjuvant endocrine therapy or cytotoxic chemotherapy were given more frequently in the SN-positive cohort than in the SN-negative cohort (84.2% vs. 5.4%, $P < 0.001$). The chemotherapy regimen was adriamycin plus cyclophosphamide followed by paclitaxel.

Prognosis between SN-positive and -negative cohorts

The median follow-up time was 73.6 months (range 11.6–102.4). In the SN-positive cohort, no patient experienced distant metastasis or breast cancer death. In the SN-negative cohort, one patient had distant recurrence in the lung; however, no patient had died of breast cancer by the last follow-up. Therefore, 7-year DDFS was 100 and 99.7% for the SN-positive and SN-negative cohorts, respectively ($P = 0.83$, Fig. 1a). Seven-year BCSS was 100% for both SN-positive and SN-negative cohorts (Fig. 1b).

Detection of occult invasion in primary tumours

Of the 19 SN-positive tumours, 11 had already undergone total step-sectioning in the previous study [4], thus, 8 tumours newly underwent step-sectioning for the present study. A total of 1421 step-sectioned H&E slides were examined for the 19 SN-positive cases (median 57; range 17–344). Of the 19 SN-positive patients, 9 (47.4%, case #1–9) were found to have occult invasions, and 7 and 2 were pT1mi disease and pT1a disease, respectively (Table 2).

Correlation between occult invasion and lymph node status

The median CK19 mRNA copy numbers in the SN were 400 copies/μL (range 260–4700) and 590 copies/μL (range 290–13,000) in patients with and without occult invasions, respectively (Table 2). Moreover, 2 (22.2%) of the 9 patients with occult invasions and 3 (30.0%) of the 10 patients without occult invasions had additional non-SN metastasis.

Of the 10 SN-positive DCIS cases without occult invasion, 4 cases (case #10–13) had low-volume metastasis confined to SNs (Table 2). However, 1 case (case #14) had macrometastasis in the SN and 5 cases (case #15–19) had micrometastasis or low CK19 mRNA expression in their non-SNs.

Predictive factor of occult invasion

Patients found to have occult invasions did not display significantly different primary tumour characteristics compared to patients without occult invasion (Table 3). In addition, as mentioned above, the number and tumour volume of SN metastasis and the incidence of non-SN metastasis were similar between patients with and without occult invasion (Table 2).

Table 1 Patient characteristics of the SN-positive and SN-negative cohorts

Characteristics	SN positive		SN negative		*P*-value
	No.	%	No.	%	
No. of patients	19	4.4	408	95.6	
Age					0.40
Median (range)	53 (27–75)		50 (26–84)		
Palpability					0.32
Palpable	6	31.6	176	43.1	
Non-palpable	13	68.4	232	56.9	
Mammographic findings					0.70[a]
Mass	3	15.8	52	12.7	
Calcification	9	47.4	209	51.2	
Architectural distortion	3	15.8	45	11.0	
Focal asymmetric density	1	5.3	33	8.1	
None	3	15.8	69	16.9	
Breast biopsy method					0.68[b]
Incisional	1	5.3	1	0.2	
Needle with vacuum-assist	10	52.6	240	58.8	
Needle without vacuum-assist	4	21.1	64	15.7	
Cytology	2	10.5	90	22.1	
Ductoscopic	2	10.5	13	3.2	
Period from breast biopsy to surgery (days)					0.20
Median (range)	83 (13–281)		64 (7–887)		
Breast surgery					0.54
Partial mastectomy	10	52.6	163	59.7	
Total mastectomy	9	47.4	110	40.3	
Pathological size (cm)					0.20
≤ 2.0	1	5.3	97	23.8	
2.1–4.0	6	31.6	122	29.9	
4.1–6.0	8	42.1	88	21.6	
> 6.0	4	21.1	101	24.7	
Comedo necrosis					0.19
Comedo	4	21.1	146	35.8	
Non-comedo	15	78.9	262	64.2	
Nuclear grade					0.59
1	14	73.7	257	63.0	
2	3	15.8	106	26.0	
3	2	10.5	45	11.0	
Oestrogen receptor					0.30
+	18	94.7	353	86.5	
−	1	5.3	55	13.5	
Progesterone receptor					0.11
+	17	89.5	298	73.0	
−	2	10.5	110	27.0	
Adjuvant systemic therapy					< 0.01**
None	3	15.8	386	94.6	
Endocrine therapy	13	68.4	22	5.4	
Cytotoxic chemotherapy	1	5.3		–	
Endocrine plus chemotherapy	2	10.5		–	

SN sentinel lymph node

**< 0.01

[a]Mass versus others

[b]Incisional and needle biopsy versus others

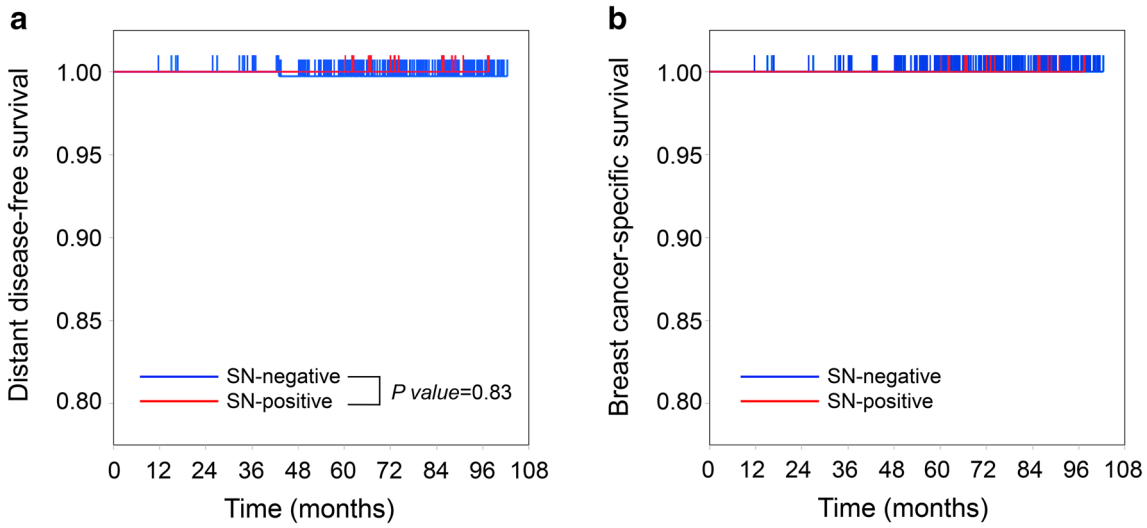

Fig. 1 Distant disease-free survival (**a**) and breast cancer-specific survival (**b**) between sentinel lymph node (SN)-positive and SN-negative cohorts

Discussion

As far as we know, the present study is the first report to combine primary tumour and lymph node status examined with comprehensive methods and clinicopathological information, in order to elucidate the prognostic impact and possible pathogenesis of nodal metastases in DCIS for improving clinical management of node-positive DCIS. This study featured exhaustive tissue-sectioning of primary tumours to detect occult invasions and a molecular whole-lymph-node analysis using the OSNA assay to accurately detect clinically relevant small metastases in the SNs and additional non-SNs.

According to our previous studies, the pathogeneses of lymph node metastases in DCIS can be either true metastasis from occult invasion between the specimen surfaces or iatrogenic dissemination of tumour or benign epithelial cells as a result of preoperative breast biopsy [4, 5]. In order to determine pathogenesis, we discuss the following four points: (1) high-risk tumour characteristics, (2) invasive biopsy methods, and (3) survival between SN-positive and SN-negative DCIS; and (4) correlation between occult invasion in the primary tumour and lymph node status in SN-positive DCIS.

Approximately 25% of patients with preoperative needle-biopsy diagnosis of DCIS upstage to invasive cancer after histopathological review of the surgical specimens [14]. Tumour characteristics with a higher likelihood of upstaging include palpable or mammographic mass, and large-size, high-grade, or comedo-type tumours [2, 14]. In the present study, however, none of these characteristics were significantly correlated with SN metastasis, which does not support true metastasis from occult invasion as the single pathogenesis.

A preoperative breast biopsy can iatrogenically displace tumour or benign epithelial cells into the lymphatic system; these dislocated cells can be passively transported to the SN and can lead to false-positive SN biopsy results [15–17]. The incidence of iatrogenic dissemination into the SN increases proportionately with the degree of invasiveness of the biopsy methods [16]. In addition, the incidence and amount of tumour displacement were inversely related to the interval from biopsy to surgery [18]. In the present study, however, no significant differences in the breast biopsy methods or the interval from biopsy to surgery were found between SN-positive and SN-negative patients, which does not support iatrogenic dissemination as the single pathogenesis.

Lymph node metastasis is one of the most powerful prognostic factors in breast cancer [19], and even micrometastasis is an independent risk factor for breast cancer mortality in early-stage breast cancer [20]. On the other hand, theoretically, iatrogenic dissemination into the SN does not have prognostic impact. In the present study, 7-year survival of SN-positive DCIS was as favourable as SN-negative DCIS. We previously reported that invasive breast cancer patients with SN metastasis < 2810 copies/μL showed similar survival to SN-negative patients [21], and most of the metastatic burden was less than this cutoff value in the present study. In addition, adjuvant systemic therapy was administered to more SN-positive patients than SN-negative patients. Therefore, low-volume metastasis may not significantly worsen the prognosis of node-positive DCIS, and/or adjuvant systemic therapy may improve their prognosis.

Additional primary tumour assessments can identify occult invasion in both SN-positive and SN-negative patients with routine postoperative diagnosis of DCIS [4, 7]. In the present study, occult invasion was identified by exhaustive

Table 2 Correlation between occult invasion and lymph node status in the sentinel node-positive DCIS, and possible pathogenesis of the lymph node metastasis

Case no.	Primary tumour						Lymph node							Overall pN	Adjuvant systemic therapy	Possible pathogenesis
	DCIS		Occult invasion				Sentinel			Non-sentinel						
	HR	HER2	Size (mm)	Final pT	HR	HER2	No. of positive/removed nodes	Maximum CK19 mRNA (copy/μL)	pN (sn)	Axillary dissection	Examination method	No. of positive/removed nodes	Maximum CK19 mRNA (copy/μL)			
1	+	−	1.0	T1mi	+	−	1/3	4700	N1mi	Level I	OSNA	2/22	7800	N1a	ET	True metastasis
2	+	−	0.2	T1mi	+	−	1/2	770	N1mi	Level I	OSNA	1/6	1000	N1mi	CT + ET	
3	+	−	2.5	T1a	+	−	1/3	620	N1mi	Level II	Histology[a]	0/15	NA	N1mi	CT + ET	
4	+	−	0.2	T1mi	+	−	1/1	530	N1mi	Sampling	Histology[a]	0/1	NA	N1mi	ET	
5	+	−	1.0	T1mi	+	−	1/6	400	N1mi	Level II	OSNA	0/14	0	N1mi	ET	
6	+	−	0.5	T1mi	+	−	1/3	310	N1mi	Level I	OSNA	0/18	4	N1mi	None	
7	+	−	2.0	T1a	+	−	1/2	280	N1mi	Level II	Histology[a]	0/11	NA	N1mi	ET	
8	+	−	0.3	T1mi	+	−	1/4	270	N1mi	Level I	OSNA	0/14	0	N1mi	ET	
9	−	+	0.1	T1mi	−	NA	1/1	260	N1mi	Level II	Histology[a]	0/12	NA	N1mi	CT	
10	+	−	ND	Tis	NA	NA	1/3	460	N1mi	Level II	OSNA	0/9	2	N1mi	ET	Iatrogenic dissemination
11	+	−	ND	Tis	NA	NA	1/2	410	N1mi	Level I	OSNA	0/13	0	N1mi	ET	
12	+	−	ND	Tis	NA	NA	1/1	410	N1mi	Sampling	Histology[a]	0/1	NA	N1mi	ET	
13	+	−	ND	Tis	NA	NA	1/1	290	N1mi	Level I	OSNA	0/17	21	N1mi	None	
14	+	−	ND	Tis	NA	NA	2/5	13,000	N1a	Level II	OSNA	0/17	50	N1a	None	Undetermined
15	+	−	ND	Tis	NA	NA	1/1	1400	N1mi	Level I	OSNA	7/15	2200	N1mi	ET	
16	+	−	ND	Tis	NA	NA	1/1	1400	N1mi	Level I	OSNA	1/15	780	N1mi	ET	
17	+	+	ND	Tis	NA	NA	1/4	780	N1mi	Level II	OSNA	0/13	150	N1mi	ET	
18	+	−	ND	Tis	NA	NA	1/1	720	N1mi	Level I	OSNA	2/15	1300	N1mi	ET	
19	+	+	ND	Tis	NA	NA	1/5	400	N1mi	Level II	OSNA	0/26	240	N1mi	ET	

DCIS ductal carcinoma in situ, *HR* hormone receptor, *HER2* human epidermal growth factor receptor-2, *ND* not detected, *NA* not available, *CK19* cytokeratin 19, *OSNA* one-step nucleic acid amplification assay, *ET* endocrine therapy, *CT* chemotherapy

[a]Permanent histology using a single-sectioned lymph node

Table 3 Characteristics between sentinel lymph node-positive tumours with and without occult invasion

Characteristics	Occult invasion (+)		Occult invasion (−)		*P*-value
	No.	%	No.	%	
No. of patients	9	47.4	10	52.6	
Age					0.35
Median (range)	51 (37–61)		55.5 (27–75)		
Palpability					0.41
Palpable	2	22.2	4	40.0	
Non-palpable	7	77.8	6	60.0	
Mammographic findings					0.60[a]
Mass	1	11.1	2	20.0	
Calcification	4	44.4	5	50.0	
Architectural distortion	3	33.3	–		
Focal asymmetric density	–		1	10.0	
None	1	11.1	2	20.0	
Breast surgery					0.81
Partial mastectomy	5	55.6	5	50.0	
Total mastectomy	4	44.4	5	50.0	
Pathological size (cm)					0.69
≤2.0	1	11.1	–		
2.1–4.0	3	33.3	3	30.0	
4.1–6.0	3	33.3	5	50.0	
>6.0	2	22.2	2	20.0	
Comedo necrosis					0.31
Comedo	1	11.1	3	30.0	
Non-comedo	8	88.9	7	70.0	
Nuclear grade					0.75
1	6	66.7	8	80.0	
2	2	22.2	1	10.0	
3	1	11.1	1	10.0	
Oestrogen receptor					0.96
+	8	88.9	10	100.0	
−	1	11.1	–		
Progesterone receptor					0.94
+	8	88.9	9	90.0	
−	1	11.1	1	10.0	
Adjuvant systemic therapy					0.34
None	1	11.1	2	20.0	
Endocrine therapy	7	77.8	8	80.0	
Cytotoxic chemotherapy	1	11.1	–		
Endocrine plus chemotherapy	2	22.2	–		
No. of step-sectioned H&E slides					
Median (range)	64 (17–344)		52.5 (39–163)		0.77

H&E heamatoxylin and eosin

[a]Mass versus others

tissue-sectioning in half of the SN-positive DCIS cases. For these cases (case #1–9), pathogenesis of nodal metastasis can possibly be explained by true metastasis from occult invasion.

However, no occult invasions were identified in the remaining half of SN-positive DCIS cases after the comprehensive primary tumour examinations. True metastasis from occult invasive lesions can possibly spread to non-SNs beyond the SN, while iatrogenic dissemination is confined to SNs [17]. Moreover, tumour or benign epithelial cell nests in the SNs, as a result of iatrogenic dissemination, are small, and these small nests are sometimes identified

only with immunohistochemical analysis [22, 17]. In the present study, pathogenesis of the 4 cases (case #10–13) can possibly be explained by iatrogenic dissemination, because their tumour burden in the SNs was of low volume and no non-SN metastasis was identified. However, the remaining 6 cases (case #14–19) cannot be explained by either of the pathogeneses, since 1 case (case #14) had macrometastasis in the SN and 5 cases (case #15–18) had micrometastasis or low CK19 mRNA expression in their non-SNs.

Therefore, pathogenesis for nodal metastasis in DCIS cannot uniformly be determined, and more than one pathogenesis seems to be associated with nodal metastasis in DCIS. In the present study, two-thirds of the pathogenesis for nodal metastasis in DCIS can possibly be explained by true metastasis from occult invasive cancer or iatrogenic dissemination by preoperative breast biopsy. However, the remaining one-third of SN-positive DCIS cannot be explained by either of the two pathogeneses. Recently, the parallel model of cancer progression has been proposed, in which tumour cells disseminate from the primary lesion in the early phase before the acquisition of fully malignant phenotypes [23]. Regarding breast cancer progression, a small pool of cancer stem cells in DCIS is speculated to directly disseminate to the lymph nodes and distant organs without local invasive recurrence [24]. Thus, the parallel progression model might be applicable to node-positive DCIS with undetermined pathogenesis.

Although some node-positive DCIS appear to be true DCIS with iatrogenic dissemination, clinicians may have to treat node-positive DCIS as node-positive small invasive breast cancers in daily practice. This is because although half of the SN-positive DCIS cases had occult invasions identified by exhaustive tissue-sectioning, it is difficult to predict occult invasions without exhaustive tissue-sectioning of primary tumours, since no predictive factor for occult invasion was found. Nonetheless, it is difficult to routinely perform tissue-sectioning due to of the heavy workload for technicians and pathologists. According to the current guideline [6], adjuvant endocrine therapy is recommended for hormone receptor-positive pT1mi/1a pN1mi tumours and chemotherapy is considered as an option for both hormone receptor-positive and receptor-negative pT1mi/1a pN1mi tumours. In addition, adjuvant endocrine therapy plus chemotherapy is recommended for hormone receptor-positive pT1mi/1a pN1a tumours and chemotherapy is recommended for hormone receptor-negative pT1mi/1a pN1a tumours. However, considering the favourable prognosis of node-positive DCIS with adjuvant endocrine therapy, the optional chemotherapy may be omittable for node-positive DCIS with pN1a disease.

In conclusion, more than one pathogenesis seems to be associated with nodal metastasis in DCIS. Two-thirds of the cases can possibly be explained by true metastasis from occult invasive cancers or iatrogenic dissemination via preoperative breast biopsy. However, the remaining one-third cannot be explained by either of these pathogeneses. Node-positive DCIS has favourable prognosis with adjuvant systemic therapy. In practical settings, clinicians may have to treat these tumours as node-positive small invasive breast cancers, since it is difficult to predict the possible pathogenesis of nodal metastasis without exhaustive tissue-sectioning of primary tumours. Prospective studies are needed to further optimize adjuvant therapy for node-positive DCIS.

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Compliance with ethical standards

Conflict of interest Futoshi Akiyama received consulting fee from Sysmex Corporation paid to the Japanese Foundation for Cancer Research. The other authors declare no conflicts of interest.

Ethical approval This study was approved by the Institutional Review Board of the Cancer Institute Hospital (Reference Nos. 2011-1015 and 2012-1061), and performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The written general consent was obtained from each of the patients.

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