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Original Article

Lesion Size on Ultrasonography Predicts Potential Invasion in Ductal Carcinoma *in situ* Preoperatively Diagnosed by Breast Needle Biopsy

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Ductal carcinoma *in situ* (DCIS) of the breast has no potential to metastasize, but over 20% of cases preoperatively diagnosed as DCIS are upstaged on final pathology. The rates of upstaging and the predictors for invasion on final pathology were evaluated. For 240 primary breast cancers, radiological findings on mammography, ultrasonography, and magnetic resonance imaging were investigated along with pathological and clinical information. Univariate and multivariate analyses were performed to identify predictors of potential invasion. Of the 240 breast cancers, 68 (28.3%) showed invasion on final pathology, and 5 (2.5%) had sentinel node metastasis. The multivariate analysis identified five independent predictors: non-mass lesions >2.4 cm on ultrasonography (odds ratio [OR] 2.84, 95% confidence interval [CI] 1.02-7.95, $p=0.047$), comedo-type histology (OR 6.89, 95% CI 1.89-25.08, $p<0.01$), solid-type histology (OR 7.97, 95% CI 2.08-30.49, $p<0.01$), palpable mass (OR 2.63, 95% CI 1.05-6.64, $p=0.04$), and bloody nipple discharge (OR 4.61, 95% CI 1.20-17.66, $p=0.02$). These five predictors were associated with invasion on final pathology and may help select candidates for sentinel node biopsy.

Key words: breast cancer, DCIS, breast needle biopsy, imaging examination, sentinel node biopsy

Breast cancer screening programs using mammography have greatly increased the detection of ductal carcinoma *in situ* (DCIS) [1]. Nowadays, approximately 20-25% of screening-detected breast cancers are DCIS [2,3]. DCIS is characterized by the proliferation of neoplastic ductal epithelial cells confined to the basement membrane of mammary ducts [4]. Since DCIS does not have the ability to metastasize to regional lymph nodes, axillary lymph node staging is theoretically not required. However, more than 20% of patients are upstaged to invasive disease on final pathology [5-9] because breast needle biopsies only sample limited parts of the lesions.

This underestimation causes problems regarding axillary lymph node metastases. Sentinel node (SN) biopsy is currently performed for clinically node-negative invasive breast cancer to evaluate axillary lymph node status [10]. However, SN biopsy for all patients with preoperatively diagnosed DCIS would lead to overtreatment; the incidence of SN metastases was found to be only 7.4% in a meta-analysis [11]. Although SN biopsy has lower morbidity than axillary resection, SN biopsy potentially causes several adverse effects such as lymphedema and motor neuropathy [12,13]. Therefore, unnecessary SN biopsy needs to be avoided.

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On the other hand, if SN biopsy is not performed for all patients, more than 20% of patients who have invasive disease will require SN biopsy later because invasive disease can lead to lymph node metastases.

To avoid both over- and undertreatments, more accurate preoperative predictors are needed. When DCIS is proven by a breast needle biopsy, breast surgeons comprehensively estimate the probability of invasive disease with clinical, pathological and imaging examinations.

In Japan, mammography, ultrasonography, and magnetic resonance imaging (MRI) are currently routinely preformed as useful preoperative imaging examinations of the breast. Contrast-enhanced MRI has been increasingly used, because MRI has high sensitivity (90-94%) for detection [14, 15] and is superior to mammography and ultrasonography in demonstrating the extent and multi-centricity of breast cancer [14, 16, 17]. There have been three reports so far in which the three modalities were all used as preoperative investigations to analyze predictors for invasive disease [9, 18, 19]. However, no report has examined which imaging size and features are the most useful to predict potential invasion. Therefore, in this single-institute retrospective study, the radiological sizes and features of DCIS on mammography, ultrasonography and MRI, in addition to pathology and clinical examinations, were analyzed in order to determine which modality has features that can accurately identify patients at higher risk of invasive disease.

Patients and Methods

Patient selection. The subjects were patients with a preoperative needle-biopsy diagnosis of DCIS who underwent breast surgery between January 2007 and April 2009 at the Cancer Institute Hospital, Tokyo, Japan. Inclusion criteria were as follows: 1) mammography, ultrasonography, and MRI procedures were all performed to evaluate primary tumor before surgery, and 2) patients were clinically and ultrasonographically node-negative before surgery. Exclusion criteria were as follows: 1) double cancer in the ipsilateral breast on final pathology, 2) neoadjuvant drug therapy for contralateral breast cancer, and 3) chemotherapy for another cancer before breast surgery. This study was approved by the Institutional Review Board of the Cancer Institute Hospital (2015-1126).

Clinical examinations. Clinical examinations were performed twice, at the initial visit and on the day before surgery. If the findings were different, those on the day before surgery were used for the study. Palpable masses included indurations due to tumors. Nipple discharge was classified as bloody, serous, or milky.

Imaging examinations. The Breast Imaging Reporting and Data System 4th Edition [20] of the American College of Radiology was used to interpret the mammographic, ultrasonographic, and MRI imaging features. Mammographic features were classified as masses, focal asymmetric densities, distortions, or calcifications. The maximum size of the calcifications was also measured. Mammography was performed with a Hologic Selenia system (Hitachi, Tokyo, Japan). Ultrasonographic features were classified as mass or non-mass abnormalities based on the Guideline for Breast Ultrasound: Management and Diagnosis 3rd Edition [21], and the maximum size of non-mass abnormalities was measured. Ultrasonography was performed with the following devices: an Aplio SSA-700A (Toshiba, Tokyo, Japan), a Nemio SSA-550A (Toshiba), an EUB-6000 (Hitachi), or an EUB-5500 (Hitachi). MRI was performed on a 1.5-T system (Signa HDx 1.5T, GE Yokogawa Medical Systems, Tokyo, Japan), and dynamic contrast-enhanced MRI, fat-suppressed T2-weight MRI, and diffusion-weighted imaging with apparent diffusion coefficient maps were reviewed. The features on MRI were classified as mass or non-mass enhancement, and the maximum size of the non-mass enhancement was measured for the most suitable image condition. When a patient had several imaging features, the higher priority one was chosen to avoid duplication.

Breast needle biopsy and histological evaluation of biopsy samples. Breast needle biopsy was performed under stereotactic or ultrasonography guidance. Stereotactic needle biopsy was mainly used for microcalcifications on mammograms using an 11-gauge Mammotome ST (Johnson & Johnson K.K., Tokyo, Japan). The sampled specimens were radiologically checked for microcalcifications. Ultrasonography-guided biopsy was used for lesions that were visible on ultrasonography. A 14-gauge Bard Monopty (Medicon, Inc., Osaka, Japan), 10-gauge Bard Vacora (Medicon, Inc.), or 11-gauge Mammotome EX (Johnson & Johnson K.K.) were used according to physician preference. The needle biopsy samples were stained with

hematoxylin and eosin, and the histological structure and the nuclear grade were evaluated [22].

Histological examination of surgical samples. Surgical materials from partial mastectomy were sectioned at 0.5-cm intervals continuously from the nipple side to the periphery, and each section was examined histologically [23]. Surgical materials from the mastectomy were sectioned at 0.5- to 0.7-cm intervals continuously from the nipple side to the periphery, and sectioning was performed to cover the entire tumor spread with macroscopic and radiologic examinations. All of the sections were examined with hematoxylin and eosin staining [24].

SN biopsy procedure. Intraoperative lymphatic mapping of SNs was achieved by a radioactive colloid and/or blue dye of indigo carmine. The radioisotope tracer used was 1.5 mCi/ml 99mTc-phytate. The tracer was injected into the intradermal and subdermal space in the tumor area and the retro-tumoral space the day prior to surgery, and lymphoscintigraphy was performed one hour after injection. Additionally, 2 to 3 ml of indigo carmine (Daiichi Sankyo, Tokyo, Japan) was injected in the peri-tumoral space or areola just before surgery. SNs were identified using a hand-held gamma-probe and blue dye staining. Excised SNs were intraoperatively sectioned at 0.2-cm intervals and examined by frozen section with hematoxylin and eosin staining [25].

Statistical analysis. Preoperative information on clinical, radiological, and pathological characteristics was compared between pure DCIS and invasive disease on final pathology. Regarding the calcification size on mammography, and the non-mass lesion size on ultrasonography and on MRI, the cutoff values were determined using Youden indexes, which are defined as the maximum vertical distance between ROC curve and diagonal line.

The univariate and multivariate logistic regression analyses were used to investigate the relationships between the preoperative information and the presence of invasive disease on final pathology. The biopsy methods and the number of specimens were excluded from the multivariate analysis, because the choice of the needle size depended on the preference of the doctor who performed the biopsy. The MRI findings of the cancer with and without bloody nipple discharge were compared. The confidence intervals (CIs) were set at 95%. A p-value of <0.05 (two-sided) was considered significant. All analyses were conducted using the statistical software package Stata12 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics. During the study period, 264 patients were initially diagnosed as having DCIS by breast needle biopsies. Of the 264 patients, 237 were ultimately included. Of the 240 tumors (3 patients had bilateral tumors), 172 (71.7%) were pathologically confirmed as pure DCIS, and 68 (28.3%) were found to be invasive on final pathology. Table 1 shows the patient characteristics by invasive status on final pathology.

Predictors of invasive disease. The cutoff values were set at 2.1 cm, 2.4 cm and 4.0 cm for the calcification size on mammography, and non-mass lesion size on ultrasonography and on MRI, respectively. On the univariate analyses, the following nine parameters were significant for invasive disease: palpable mass, bloody nipple discharge, mass or focal asymmetric density on mammography, non-mass lesion >2.4 cm in size on ultrasonography, non-mass lesion >4.0 cm in size on MRI, mass lesion on MRI, solid-type histology and comedo-type histology, and high nuclear grade (Table 2).

The multivariate analysis showed that the following 5 factors were independent predictors: palpable mass (odds ratio [OR] 2.63, 95% CI 1.05-6.64, $p=0.04$), bloody nipple discharge (OR 4.61, 95% CI 1.20-17.66, $p=0.02$), comedo-type histology (OR 6.89, 95% CI 1.89-25.08, $p<0.01$), solid-type histology (OR 7.97, 95% CI 2.08-30.49, $p<0.01$), and non-mass lesion >2.4 cm in size on ultrasonography (OR 2.84, 95% CI 1.02-7.95, $p=0.047$) (Table 2).

MRI findings of tumors presenting bloody nipple discharge. Tumors presenting bloody nipple discharge occupied wider lesions than those without (Table 3). The rate of non-mass lesions (>4.0 cm in size) on MRI was 52.2% in the group of cancers presenting nipple discharge. In addition, almost all of the cancers (12 of 13 cases) with bloody nipple discharge had small invasions (<0.5 cm in size) (median 0.1 cm, range 0.1-1.3 cm).

Axillary staging by SN biopsy. Of the 240 tumors, 202 (81.2%) underwent SN biopsy (Table 1). Of the 202 tumors, 5 (2.5%) had positive SN(s), and all five patients underwent additional axillary lymph node

Table 1 Correlation between patient characteristics and invasive disease on final pathology

Characteristic	No.	%	Invasive disease		Pure DCIS	
			No.	%	No.	%
No. of patients	240	100.0%	68	28.3%	172	71.7%
Age (years)						
Median (range)	49 (20–80)		49 (29–77)		49 (20–80)	
Laterality						
Right	109	45.4%	30	27.5%	79	72.5%
Left	131	54.6%	38	29.0%	93	71.0%
Tumor location						
Upper inner	53	22.1%	16	30.2%	37	69.8%
Lower inner	19	7.9%	5	26.3%	14	73.7%
Upper outer	119	49.6%	31	26.1%	88	73.9%
Lower outer	41	17.1%	13	31.7%	28	68.3%
Central	8	3.3%	3	37.5%	5	62.5%
Biopsy device						
14-gauge Bard Monopty	33	13.8%	15	45.5%	18	54.5%
11-gauge Mammotome EX	195	81.3%	51	26.2%	144	73.8%
10-gauge Bard Vacora	12	5.0%	2	16.7%	10	83.3%
Image guidance						
Stereotactic	164	68.3%	39	23.8%	125	76.2%
Ultrasonography-guided	76	31.7%	29	38.2%	47	61.8%
No. of biopsy specimens						
Median (range)	5 (1–16)		5 (1–12)		5 (1–16)	
Palpation						
No finding	176	73.3%	37	21.0%	130	79.0%
Mass	64	26.7%	31	48.4%	33	51.6%
Nipple discharge						
None or milky	213	88.8%	53	24.9%	160	75.1%
Serous	4	1.7%	2	50.0%	2	50.0%
Bloody	23	9.6%	13	56.5%	10	43.5%
Mammography						
Calcification (≤2.1 cm)	91	37.9%	18	19.8%	73	80.2%
Calcification (>2.1 cm)	77	32.1%	24	31.2%	53	68.8%
Distortion	14	5.8%	4	28.6%	10	71.4%
Mass or FAD	30	12.5%	13	43.3%	17	56.7%
No finding	28	11.7%	9	32.1%	19	67.9%
Ultrasonography						
No finding	97	40.4%	18	18.6%	79	81.4%
Non-mass (≤2.4 cm)	58	24.2%	14	24.1%	44	75.9%
Non-mass (>2.4 cm)	54	22.5%	26	48.1%	28	51.9%
Mass	31	12.9%	10	32.3%	21	67.7%
Magnetic resonance imaging						
No finding	68	28.3%	13	19.1%	55	80.9%
Non-mass (≤4.0 cm)	96	40.0%	25	26.0%	71	74.0%
Non-mass (>4.0 cm)	54	22.5%	19	35.2%	35	64.8%
Mass	22	9.2%	11	50.0%	11	50.0%
Histological structure						
Low papillary or flat	55	22.9%	5	9.1%	50	90.9%
Cribriform	62	25.8%	12	19.4%	50	80.6%
Papillary	15	6.3%	4	26.7%	11	73.3%
Solid	35	14.6%	18	51.4%	17	48.6%
Comedo	73	30.4%	29	39.7%	44	60.3%
Nuclear grade						
1	156	65.0%	34	21.8%	122	78.2%
2	59	24.6%	25	42.4%	34	57.6%
3	25	10.4%	9	36.0%	16	64.0%
Breast surgery						
Total mastectomy	127	52.9%	49	38.6%	78	61.4%
Partial mastectomy	113	47.1%	19	16.8%	94	83.2%
Axillary surgery						
None	36	15.0%	4	11.1%	32	88.9%
Sentinel node biopsy only	197	82.1%	57	28.9%	140	71.1%
Complete axillary resection	7	2.9%	7	100.0%	0	0.0%

DCIS, ductal carcinoma *in situ*; FAD, focal asymmetric density.

Table 2 Uni- and multivariable analysis of invasive disease on final pathology

Characteristic	Univariable				Multivariable			
	Odds ratio	95% CIs		*P*-value	Odds ratio	95% CIs		*P*-value
		Lower	Upper			Lower	Upper	
Age (years)								
≤40	1.00	(reference)			1.00	(reference)		
41–50	0.75	0.33	1.72	0.50	0.57	0.20	1.60	0.29
≥51	0.76	0.34	1.71	0.51	0.52	0.19	1.44	0.21
Laterality								
Right	1.00	(reference)			1.00	(reference)		
Left	1.08	0.61	1.89	0.80	1.12	0.57	2.21	0.74
Tumor location								
Upper inner	1.00	(reference)			1.00	(reference)		
Lower inner	0.83	0.25	2.68	0.75	1.00	0.24	4.13	1.00
Upper outer	0.81	0.40	1.67	0.57	0.81	0.34	1.94	0.64
Lower outer	1.07	0.44	2.59	0.87	1.06	0.37	3.00	0.92
Central	1.39	0.30	6.52	0.68	0.41	0.04	4.26	0.45
Palpation								
No finding	1.00	(reference)			1.00	(reference)		
Mass	3.53	1.92	6.49	<0.01**	2.63	1.05	6.64	0.04*
Nipple discharge								
None, milky or serous	1.00	(reference)			1.00	(reference)		
Bloody	3.83	1.59	9.23	<0.01**	4.61	1.20	17.66	0.02*
Mammography								
Calcification (≤2.1 cm)	1.00	(reference)			1.00	(reference)		
Calcification (>2.1 cm)	1.84	0.91	3.72	0.09	1.06	0.45	2.51	0.89
Distortion	1.62	0.46	5.77	0.46	0.51	0.09	2.81	0.44
Mass or FAD	3.10	1.28	7.53	0.01*	1.09	0.27	4.30	0.91
No finding	1.92	0.75	4.95	0.18	0.38	0.08	1.74	0.21
Ultrasonography								
No finding	1.00	(reference)			1.00	(reference)		
Non-mass (≤2.4 cm)	1.40	0.63	3.08	0.41	1.17	0.46	3.00	0.75
Non-mass (>2.4 cm)	4.08	1.95	8.54	<0.01**	2.84	1.02	7.95	0.047*
Mass	2.09	0.84	5.19	0.11	0.76	0.15	3.72	0.66
Magnetic resonance imaging								
No finding	1.00	(reference)			1.00	(reference)		
Non-mass (≤4.0 cm)	1.49	0.70	3.18	0.30	0.82	0.32	2.09	0.67
Non-mass (>4.0 cm)	2.30	1.01	5.23	0.05*	0.62	0.19	1.98	0.42
Mass	4.23	1.51	11.87	<0.01**	2.62	0.51	13.44	0.25
Histological structure								
Low papillary or flat	1.00	(reference)			1.00	(reference)		
Cribriform	2.40	0.79	7.32	0.12	2.26	0.63	8.16	0.21
Papillary	3.64	0.84	15.78	0.09	2.72	0.52	14.29	0.24
Solid	10.59	3.41	32.89	<0.01**	7.97	2.09	30.49	<0.01**
Comedo	6.59	2.35	18.50	<0.01**	6.89	1.89	25.08	<0.01**
Nuclear grade								
1	1.00	(reference)			1.00	(reference)		
2	2.64	1.39	5.01	<0.01**	1.44	0.60	3.46	0.42
3	2.02	0.82	4.97	0.13	0.76	0.21	2.27	0.68

CI, confidence interval; FAD, focal asymmetric density; *$p < 0.05$; **$p < 0.01$.

Table 3 Magnetic resonance imaging findings of tumors with and without bloody nipple discharge

	Bloody nipple discharge					
	Present		Absent		Total	
Finding	No.	%	No.	%	No.	%
No finding	3	13.0	65	30.0	68	28.3
Non-mass (≤4.0 cm)	4	17.4	92	42.4	96	40.0
Non-mass (>4.0 cm)	12	52.2	42	19.4	54	22.5
Mass	4	17.4	18	8.3	22	9.2
Total	23	100.0	217	100.0	240	100.0

resection. One of them had one metastatic node among the non-sentinel lymph nodes. No metastasis was found in the patients with pure DCIS on final pathology. Two of the patients initially underwent axillary resection because axillary metastases were preoperatively proven by fine needle aspiration cytology. These 2 tumors both showed palpable masses, comedo-type histology, and a size >4.0 cm on all three imaging examinations.

Discussion

The present study focuses on the utility of mammography, ultrasonography, and MRI to predict the potential invasion of preoperatively diagnosed DCIS. Radiological findings including the tumor size (*i.e.* calcifications on mammography, non-mass abnormalities on ultrasonography, and non-mass enhancement on MRI) were used as variables for this analysis. Five independent predictors were identified: large non-mass abnormalities on ultrasonography (>2.4 cm in size), histological structure (comedo type and solid type), and clinical examination (palpable mass and bloody nipple discharge).

Thus, ultrasonographic tumor size is one of the useful predictors for potential invasion. Lee *et al.* reported that a lesion size >2.0 cm on ultrasonography was a significant predictor [7]. Larger non-mass abnormalities on ultrasonography could more likely contain invasive disease than larger calcification on mammography and larger non-mass-like enhancement on MRI—findings that mainly suggest intraductal components [7]. Larger non-mass abnormalities on ultrasonography tend to indicate a thicker lesion, which could be associated with invasive disease. These radiological variations may be caused by the different expressions on each modality to reflect various characteristics of the tumors: for example, the hardness and calcifications on mammography, the amount of tumor cells on ultrasonography, and the blood flow on MRI. In the present study, the finding of a mass or focal asymmetric density on mammography and a mass on MRI were both significant on the univariate analysis but not on the multivariate analysis. This is probably because a mass on imaging examination was interrelated with a palpable mass.

With regard to the needle size, DCIS can be diagnosed more correctly when using a 10- or 11-gauge needles than a 14-gauge needle. This is partly because the 14-gauge needles tend to be used for radiologically clear lesions on ultrasonography, and the 10- or 11-gauge needles for radiologically obscure lesions such as tumors only presenting calcifications.

Clinical examination factors were found to be useful predictors for potential invasion. A palpable mass was the common predictor in the previous reports [5,8,9,23,26]. Bloody nipple discharge has usually been considered to suggest a benign condition such as papilloma or ductal ectasia but also DCIS and DCIS with microinvasion [27]. The present study suggests that tumors presenting bloody nipple discharge are underestimated by needle biopsies because they histologically have small invasion within the wide range of intraductal lesions.

The histological structures of intraductal components are also common predictors. In the present study, comedo-type and solid-type histology were both identified as independent predictors. Comedo-type histology is a well-known predictor [28]. Osako *et al.* and Han *et al.* reported that solid type was also a significant predictor [23,29]. Solid-type intraductal lesions grow expansively in the mammary duct, so they may potentially have more chances to invade the stroma.

In the present study, 28.3% of the patients had invasive disease on final pathology, which is almost the same rate as in previous studies (20-41%) [5-9]. The rate of a positive SN biopsy was lower (2.5%) than that in the previous meta-analysis [11], and all five patients who had SN metastases had invasive disease on final pathology. The results of the American College of Surgeons Oncology Group Z0011 trial [30] suggested that not all lymph node metastases result in recurrence or systemic metastases. Therefore, we might not need to undertake SN biopsy on all patients who are found to have occult invasive diseases on final pathology. If so, further studies are needed to determine which patients can forego the SN biopsy.

Our study has two limitations. One limitation is inherent to any single-institutional, retrospective study. The other is that several types of ultrasonography machines were used in this study. In conclusion, preoperative findings of ultrasonography (non-mass abnormalities >2.4 cm in size), histopathology (comedo type and solid type), and clinical examinations (palpable masses and bloody nipple discharge) were associated with potential invasion on final pathology by multivariate analysis. These predictors are useful to determine the necessity of SN biopsy for patients with DCIS diagnosed by breast needle biopsy.

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