

Predictors for upstaging of ductal carcinoma *in situ* (DCIS) to invasive carcinoma in non-mass-type DCIS

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Abstract. Preoperatively diagnosed ductal carcinoma *in situ* (DCIS) is sometimes upstaged to invasive cancer by post-operative pathological examination. Various preoperative factors associated with upstaging to invasive cancer have been reported; however, this subject remains to be clarified. DCIS takes various forms on imaging, but many cases show non-mass-type lesions. In non-mass-type DCIS, recognizing the presence of invasion is difficult. To investigate predictors associated with upstaging to invasive cancer more precisely, we examined only non-mass-type DCIS. The present study retrospectively analyzed 101 patients diagnosed with non-mass-type DCIS preoperatively on breast biopsy at our institution between 2007 and 2017. Data were analyzed using Fisher's exact probability test and two-sample t-tests. Multivariate analysis was performed using logistic regression. The results showed that 27 patients (27%) were finally diagnosed with invasive cancer. Univariate analysis revealed abnormal result of palpation on breast examination (P=0.05), comedo necrosis (P=0.05), and HER2 status (P=0.02) as significant predictors. Multivariate analysis revealed an abnormal result of palpation as an independent predictor of invasive cancer underestimation (odds ratio 4.76; confidence interval 1.44-15.7; P=0.01). In conclusion, preoperatively diagnosed non-mass-type DCIS represented an underestimation in approximately 27% of cases. In particular, the presence of a clinically abnormal palpation increases the chance of upstaging to invasive cancer.

Introduction

Ductal carcinoma *in situ* (DCIS) is a non-invasive malignant breast disease described as a precursor lesion to invasive breast cancer. With the progress of diagnostic breast imaging, opportunities to diagnose DCIS are on the increase.

If breast cancer is suspected, core-needle biopsy (CNB) or vacuum-assisted biopsy (VAB) is performed. Those percutaneous breast biopsies are important procedures for decreasing the number of excisional biopsies. However, diagnosis from such a biopsy cannot provide definitive diagnosis. For example, a preoperative diagnosis of DCIS is sometimes upstaged to invasive ductal carcinoma (IDC). In the literature, the underestimation rate has been reported as 15-40% (1-4).

Upstaging to IDC is critical for both patients and surgeons. Surgeons should consider the possibility of underestimation, such as whether to include sentinel lymph node biopsy (SLNB) in a subsequent definitive surgical procedure. Some predictors of underestimation have been reported. Brennan *et al* reported palpability, nuclear grade, tumor size, and other factors (2). However, reliable predictors have not been clearly identified.

DCIS takes various forms, including solid mass lesion, intracystic lesion, calcification alone, and distortion. An abnormal result from palpation is sometimes a predictor of upstaging to invasive disease (5). However, for lesions showing an intracystic component, the underestimation ratio may not necessarily be high even if the results of palpation are abnormal. Investigating mass-type DCIS or non-mass-type DCIS (Fig. 1) separately is thus important.

This case focused on predictors for underestimation of non-mass-type lesions. Currently, no reports from this point of view have been published. This is thus, to the best of our knowledge, the first report to investigate underestimation, defined as biopsy diagnosis of DCIS with attention only on non-mass-type lesions.

Patients and methods

Patients. The present study was conducted with approval from the institutional review board of Tokyo Medical and Dental University (IRB-approved number is M2000-831, 2000) and with informed consent of the patient. Data were retrieved from

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Abbreviations: DCIS, ductal carcinoma *in situ*; CNB, core-needle biopsy; VAB, vacuum-assisted biopsy; MRI, magnetic resonance imaging; US, ultrasound; Gd-DTPA, gadobenate dimeglumine; MMG, mammography; ST-VAB, stereotactic VAB; ER, estrogen receptor; PgR, progesterone receptor; IHC, immunohistochemistry; FAD, focal asymmetric density

Key words: breast cancer, DCIS, non-mass-type DCIS

our database for 150 consecutive women with an initial CNB or VAB diagnosis of DCIS, and who underwent surgical resection at our institution between September, 2007 and August, 2017. Only 101 cases in which masses could not be confirmed from magnetic resonance imaging (MRI) and ultrasound (US) were examined (Fig. 1).

Non-mass-type lesions were defined from US showing a non-mass lesion (e.g., duct ectasia, intraductal calcification, architectural distortion, clustered microcysts, hypoechoic area) and MRI showing non-mass enhancement (homogeneous, heterogeneous, clumped, or clustered ring). A lack of abnormal findings on US and/or MRI were also considered acceptable.

Imaging evaluation. Mammography examination (cranio-caudal and mediolateral oblique views) was performed using a Lorad Selenia mammograph (Hologic). An EUB-7500 scanner with a EUP-L54MA 9.75-MHz linear probe (Hitachi Medical Systems) or Aplio XG scanner with a PLT-805AT 8.0-MHz linear probe (Toshiba Medical Systems) was used for US examinations. MRI examination was performed with a 1.5-T system (Magnetom Vision; Siemens) and a 3.0-T system (Signa HDxt; General Electric Medical Systems) using a breast coil in the prone position. To evaluate the results of MRI, the early phase of a contrast enhancement study within 1 and 2 min after intravenous bolus injection of gadobenate dimeglumine (Gd-DTPA) (0.2 ml/kg) was obtained. A unilateral coronal T1-weighted sequence [repetition time (TR) = 170 msec; echo time (TE) = 4.7 msec; flip angle = 40°; 4-mm thick section, 256x256 matrix; field of view = 210 mm] using the 1.5-T system and bilateral axial fat-suppressed T1-weighted sequence (TR = 6.5 msec; TE = 2.4 msec; flip angle = 10°; section thickness = 2 mm; matrix = 512x512; field of view = 360 mm) using the 3.0-T system were employed.

Examinations were performed by one of three radiologists with >5 years of experience in breast imaging. The radiologists had knowledge of the clinical indications for examination and interpreted lesions using the Breast Imaging Reporting and Data System. For each lesion, the two most experienced radiologists retrospectively reviewed the results together to reach consensus.

Biopsy procedure. CNB or VAB were performed, guided by US or mammography (MMG). If lesions were detected by US, biopsy was performed as a US-guided procedure. If no lesion was detected by US, stereotactic VAB (ST-VAB) was performed. CNB used a 14-G Biopsy System (CR Bard) and VAB used needles of 10 G8- or 11-G Mammutome (Ethicon Endo-Surgery) or 11- or 14-G Vacora (CR Bard). Our standard protocol was to obtain 3-7 core samples per lesion in the US-guided procedure and 5-12 core samples in ST-VAB. In specific cases such as where the amount of tissue obtained was grossly inadequate or targeting difficulty was experienced, the number of samples was increased. On the other hand, when the patient proved uncooperative or declined to continue, or when minor complications such as pain or bleeding were encountered, fewer core samples were obtained. Cases of excisional biopsy were excluded.

Immunohistochemical examination. All specimens were analyzed by pathologists from Tokyo Medical and Dental

university, and specimens were considered estrogen receptor (ER)- or progesterone receptor (PgR)-positive on immunohistochemistry (IHC) for staining rates >10%. For HER2 receptor values, IHC 3+ was defined as breast cancer with strong, complete membrane staining observed in at least 10% of tumor cells. For HER2 receptor overexpression of 2+, gene amplification with fluorescence *in situ* hybridization was not performed in this study.

Data analysis. After review of the postoperative pathologic results, final diagnoses of all lesions were divided into two groups: Pure DCIS, or invasive ductal carcinoma. Medical records were then reviewed. Differences in proportions of categorical data were tested using Fisher's exact probability test. Unless otherwise indicated, significant differences among mean values of numerical data were analyzed using the two-sample two-sided t-test. Predictors of invasive carcinoma underestimation were determined by uni- and multivariate logistic regression analyses. Values of $P < 0.05$ were regarded as statistically significant. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, (<http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html>), and a graphic user interface for R (The R Foundation for Statistical Computing). More precisely, EZR is a modified version of R Commander designed to add statistical functions frequently used in biostatistics (6).

Results

Clinicopathological characteristics. The clinicopathological features of all patients are summarized in Table I. The mean age of all patients was 55 years (range, 33-82 years). A total of 27 patients (27%) were finally diagnosed with invasive cancer. In breast examinations, results of palpation were normal in 81 patients (80%) and abnormal in 20 patients (20%). Mammographic abnormality detected calcification (cal) only in 62 patients (61%), focal asymmetric density (FAD) only in 8 patients (8%), distortion only in 6 patients (6%), negative findings in 16 patients (16%), and other (FAD+cal, FAD+distortion, or distortion+cal) in 9 patients (9%).

Enhancement patterns on MRI were categorized as follows: Homogeneous, heterogeneous, clumped, or clustered ring pattern. Enhancement patterns were homogeneous in 1 patient (1%), heterogeneous in 12 patients (12%), clumped in 44 patients (43%), and clustered ring in 32 patients (32%).

Median maximum diameter in the 90 patients with measurable lesions on MRI was 46 mm (range, 10-80 mm). The remaining 11 patients had negative findings for the breast or unmeasurable findings on breast MRI. As 30 mm was the median, we divided cases into >30 or ≤30 mm. Twenty-eight patients (28%) underwent CNB guided by US, 39 patients (39%) underwent VAB guided by US, and 34 patients (34%) underwent ST-VAB. All patients underwent SLNB, revealing a positive result in only 1 patient. No evidence of metastasis to a non-sentinel lymph node was identified.

Immunohistochemical examination. The frequency of a HER2 score of 0-2+ was 72% and that of 3+ was 20%. HER2 score

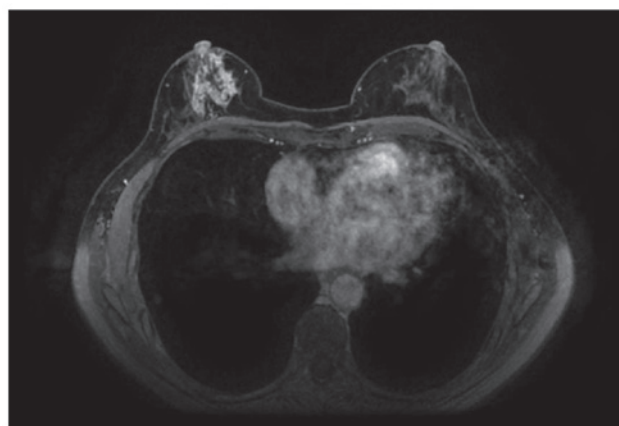
Table I. Characteristics at the time of biopsy (n=101).

Characteristics	Patients (n=101)	Percentage of sample (%)
Age (years)		
Mean age \pm SD	56.0 \pm 11.2	
≤50	40	40
>50	61	60
Postoperative pathology		
DCIS	74	73
IDC	27	27
Physical examination		
Abnormal result of palpation	20	20
Normal result of palpation	81	80
Mammographic lesion		
Calcification	62	61
FAD	8	8
Distortion	6	6
Others	9	9
No findings	16	16
Enhancement pattern on MRI		
Homogenous	1	1
Heterogenous	12	12
Clumped	44	43
Clustered ring	32	32
No findings	9	9
Maximum lesion size (mm)		
Mean diameter \pm SD	46	
Range, 10-80 mm		
10-29	25	24
30-49	39	38
50-69	21	21
>70	4	4
Other	13	13
Biopsy method		
US-CNB	28	28
US-VAB	39	38
ST-VAB	34	34
ER		
Positive	71	70
Negative	25	25
Unknown	5	5
PgR		
Positive	65	64
Negative	31	31
Unknown	5	5
HER2		
Positive	20	20
Negative	73	72
Unknown	8	8
Nuclear grade		
1,2	87	86
3	10	10
Unknown	4	4

Table I. Continued.

Characteristics	Patients (n=101)	Percentage of sample (%)
Comedo necrosis		
Absent	63	62
Present	37	37
Unknown	1	1

DCIS, diagnosed ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; FAD, focal asymmetric density; US, ultrasonography; CNB, core-needle biopsy; VAB, vacuum-assisted biopsy; MRI, magnetic resonance imaging; ER, estrogen receptor; PgR, progesterone receptor; SD, standard deviation.

Figure 1. Axial contrast-enhanced T1-weighted fat-suppressed MR subtraction images for DCIS of the right breast demonstrating non-mass-like enhancement. DCIS, diagnosed ductal carcinoma *in situ*.

was unknown in 8%. ER- and PR-positive statuses were seen in 70 and 64% of our cases.

ER+/HER2- status was seen in 64%, ER+/HER2+ status in 9%, ER-/HER2+ status in 10%, and ER-/HER2- in 5%. Among the 19 patients diagnosed with HER2-positive DCIS preoperatively, 9 patients (53%) were upstaged to IDC.

Predictors of invasive carcinoma underestimation. Univariate analysis of predictors for the presence of invasive components within final specimens initially diagnosed as DCIS is summarized in Table II. The rate of upstaging to invasive cancer in the final pathology was significantly associated with variables such as abnormal results of palpation on breast examination (P=0.05), comedo necrosis (P=0.05), and HER2 status (P=0.02). Multivariate analysis of all factors identified as significant in univariate analyses demonstrated the presence of abnormal palpation as an independent predictor of invasive cancer underestimation (odds ratio 4.76; confidence interval 1.44-15.7; P=0.01) (Table III).

Discussion

To the best of our knowledge, this is the first report to assess predictive factors focusing only on non-mass-type DCIS.

Table II. Univariate analysis of predictors of invasive cancer in all 101 patients with an initial diagnosis of non-mass DCIS.

Characteristics	Final diagnosis		Underestimation rate (%)	P-value ^a
	IDC (n=27)	DCIS (n=74)		
Age				
Mean age ± SD	54.3±10.1	55.4±11.7		0.64 ^b
Range	39-71	33-82		
Palpation				
Abnormal	9	11	45	
Normal	18	63	22	0.05
Biopsy method				
ST-VAB	8	26	23	
US-VAB	11	28	28	
US-CNB	8	20	28	0.88
MMG				
Calcification only or normal	20	58	26	
FAD	2	6	25	
Distortion	1	5	17	
Others	4	5	44	0.65
Enhancement pattern on MRI	0	1		
homogenous				
Heterogenous	5	7		
Clumped	10	34		
Clustered ring	10	22		
No findings	1	8		0.483
MRI size (mm)				
<30	12	38	24	
≥30	14	34	29	
Unknown	1	2		0.81
ER				
Positive (≥10%)	19	58	25	
Negative	8	14	36	
Unknown	0	2		0.48
PgR				
Positive (≥10%)	18	52	26	
Negative	9	20	31	
Unknown	0	2		
HER2				
Positive	10	9	53	
Negative	16	59	21	
Unknown	1	6		0.02
Nuclear grade				
3	3	7	30	
1, 2	21	65	24	
Unknown	3	2		0.71
Comedo necrosis				
Present	14	23	25	
Absent	12	51	19	
Unknown	1	0		0.05

^aP-values were estimated using Fisher's exact probability test; ^bStudent's t-test. DCIS, diagnosed ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; FAD, focal asymmetric density; US, ultrasonography; CNB, core-needle biopsy; ST-VAB, stereotactic vacuum-assisted biopsy; MRI, magnetic resonance imaging; ER, estrogen receptor; PgR, progesterone receptor; SD, standard deviation.

Table III. Multivariate analysis for predictors of invasive cancer in patients with non-mass-type DCIS (n=101).

Independent predictors of invasive cancer	Odds ratio	95% confidence interval	P-value ^a
Abnormal palpation	4.76	1.44-15.7	0.01
Comedo necrosis	2.32	0.76-7.14	0.14
CNB HER2	2.84	0.85-9.46	0.09

^aCalculated by multivariate analysis with logistic regression modeling. DCIS, diagnosed ductal carcinoma *in situ*; CNB, core-needle biopsy.

Our study showed that among preoperatively diagnosed non-mass-type DCIS, approximately 27% were underestimations. In particular, the presence of a clinically abnormal result of palpation appeared to increase the chance of up-staging to invasive cancer.

Many studies have reported preoperative factors that can predict upstaging of DCIS to invasive cancer (2,3,5,7-15). We hypothesized that the factors listed in those reports may be influenced by the forms of DCIS. Factors such as size and existence of a palpable lesion depend on whether the DCIS is mass or non-mass type. For example, among intracystic lesions, the underestimation rate may not be high despite the large, palpable lesion. Our study focused only on non-mass-type DCIS and evaluated preoperative clinicopathological factors predicting underestimation.

The underestimation rate for percutaneous breast biopsy has been reported to range between 15 and 40% (1-4). In the present study, the underestimation rate was 27%, within the reported range. As biopsy targeted at the component considered invasive is difficult for non-mass-type DCIS, we thought that the underestimation rate may be lower. However, the underestimation rate was unchanged in the present study. The underestimation rate may also change depending on the thickness of the needle, the number of specimens and the number of stereotactic biopsies, thus re-examination of an increased number of cases is necessary.

Findings of this study demonstrated that preoperative factors predictive of the invasive component were abnormal results of palpation, HER2-positive, and comedo necrosis in univariate analysis. Overexpression of HER2 in invasive breast cancer is an independent predictor of poor prognosis. The significance of HER2 overexpression in DCIS is not well defined. However, HER2 DCIS has recently been reported as an aggressive type (16-18). Monabati *et al* reported that HER2-positive DCIS cases were more likely to be of high nuclear grade (18). Mustafa *et al* reported that HER2-positive DCIS tended to be upstaged to invasive ductal carcinoma (16). However, the targets of that report were all typed as DCIS. This was the first report to examine HER2 score for non-mass-type DCIS only. The results showed that HER2-positive DCIS tended to be upstaged to invasive cancer, but no significant difference was observed in multivariate analysis. Future studies will accumulate data for these tests from additional cases and further assessment is needed for validation.

In our study, only an abnormal result of palpation was a predictive factor in multivariate analysis. Other studies have reported abnormal palpation as a predictor (1,15,18). On the other hand, Sato *et al* described abnormal palpation as irrelevant to the presence of invasion (5). However, those reports all

examined all-type DCIS, rather than restricting investigation to only non-mass-type DCIS. No previous reports have described abnormal palpation as a predictor in non-mass-type DCIS.

Previous findings have shown that, CNB and thinner needles as significant predictors of underestimation compared to VAB or thicker needles (10). In the present study, different devices were not associated with upstaging. Various factors may have contributed to this finding. One was the difference in the number of cases. Another case involved US guidance in which a lesion with suspected invasiveness was biopsied using CNB rather than VAB. As a result, the risk of underestimation tended to be reduced with VAB.

The present study has some limitations. First, this study is a single-institution review and retrospective. Nevertheless, the results of the present study may be valuable to other institutions at the time of surgery for cases with a preoperative diagnosis of DCIS. In particular, information containing HER2 status is considered valuable, as our institution routinely tests for the overexpression of HER2 in all patients with DCIS. Second, the number of cases has been reduced by targeting only non-mass DCIS. As a result, the essential stratification in this study indicated the sample size of each group was reduced. Future validation studies with a large sample set evaluating the risk factors leading to upstaging of DCIS and potential new options in the DCIS treatment algorithm are required.

In conclusion, preoperatively diagnosed non-mass-type DCIS represented an underestimation in approximately 27% of cases. In particular, the presence of a clinically abnormal result of palpation increases the chances of up-staging to invasive cancer. In cases with an abnormal result from palpation, the surgeon should select the operation in consideration of the possibility of upstaging to IDC. Larger, multi-institutional investigations are necessary to more closely examine risk factors for upstaging of non-mass-type DCIS on breast biopsy to IDC on the final pathology.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

GO performed surgery, wrote the manuscript, analyzed the data and performed the statistical analysis. TN, AO, YK, TH, HS and TI performed surgery and collected data. MM, TF and KK were responsible for diagnostic imaging and biopsy. IO was in charge of the pathology. HU designed the present study and wrote the manuscript. The final version was read and adopted by all the authors.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Tokyo Medical and Dental University Hospital (Tokyo, Japan). Signed informed consents were obtained from the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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