T1-T2 Breast Cancer with Nodal Metastasis: Characteristics of pN2 or Higher Disease Compared to pN1 Disease

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Abstract. *Aim: The objective of the present study was to evaluate the clinical and imaging characteristics of T1-T2 breast cancer with nodal metastasis and compare these features of pN2 or higher disease against those of pN1 disease. Patients and Methods: The mammographic, ultrasonographic and magnetic resonance imaging MRI features of 163 patients with T1-T2 cancer and nodal metastasis were retrospectively reviewed by two radiologists in consensus and compared between pN1 and pN2, or higher disease. Their clinical features were also compared. Results: T1-T2 cancer with pN2 or higher disease is more likely to present with pleomorphic or linear-branching calcifications (p=0.003) on mammography and have non-parallel orientation on ultrasonography (p=0.008). Invasive tumor size larger than 2 cm (p=0.032), high histological grade (p=0.002) and lymphovascular invasion (p=0.009) were significantly associated with pN2 or higher disease. Conclusion: Being familiar with the imaging characteristics of T1-T2 cancer with nodal metastasis may be helpful in preoperatively evaluating the extent of nodal disease.*

The evaluation of potential axillary lymph node metastases is important in the management of patients with breast cancer because the extent of regional disease influences the need for adjuvant chemotherapy and radiation therapy (1). In order to make treatment decisions, the distinction between pN1 (one to three metastatic lymph nodes) and pN2 (four to nine metastatic lymph nodes) or higher disease is important in node staging because locally advanced breast cancer generally requires for adequate adjuvant chemotherapy (2).

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Ultrasonography (US) has been widely used to assess the axillary lymph node status in the preoperative setting. However, predicting nodal metastasis in patients with small breast carcinomas is challenging because the diagnostic accuracy of US or US-guided fine-needle aspiration (FNA) decreases with decreasing primary tumor size (3). Abe *et al*. reported on a sensitivity of 29-69% for axillary US-guided FNA in diagnosing metastatic disease with tumors that were 5 cm or less, whereas the sensitivity was 100% in tumors that were larger than 5 cm (4). In a study by Neal *et al*., 14 out of 208 axillae (6.7%) with negative findings on US had pN2 or pN3 metastatic disease (2). These 14 false-negative cases were mainly of small breast carcinomas, and their primary tumor categories were as follows: T1 (tumor is 2 cm or less), eight patients; T2 (tumor is more than 2 cm but no more than 5 cm), five patients; and T3 (tumor is more than 5 cm), one patient.

According to the American Society of Clinical Oncology guidelines, sentinel node biopsy is acceptable for staging in most women with clinically-negative axillary lymph nodes (5). Although sentinel node biopsy usually works well, there is a potential for false-negative results. Fraile *et al*. validated sentinel node biopsies and found a false-negative rate ranging from 1% to 15% (6).

Many researchers reported that the clinicopathological features of primary breast cancer, such as large tumor size, high tumor grade, young age and lymphovascular invasion, are predictive of nodal metastasis (7-10). However, the association between the imaging characteristics of primary breast cancer and nodal metastasis, particularly the extent of nodal metastasis, remains unclear.

In the present study, we hypothesized that a better understanding of the clinical and imaging characteristics of primary cancer may be helpful in assessing the extent of nodal disease. It will be especially helpful in patients with small breast carcinomas that may be at higher risk for under-estimation of node staging by sentinel node biopsy alone than patients with large breast carcinomas.

The aim of the present retrospective study was to evaluate the clinical and imaging features of T1-T2 breast

cancer with nodal metastasis, and to compare the mammographic, ultrasonographic and magnetic resonance imaging characteristics of pN2 or higher metastatic disease with pN1 metastatic disease.

Patients and Methods

Patient selection and data collection. This study was approved by our Institutional Review Board (KUH1140071), and the requirement for informed consent was waived. A retrospective search of radiological computer records and electronic medical records at our institution identified 931 consecutive patients with newly diagnosed invasive breast cancer who underwent baseline imaging with all three imaging techniques (mammography, ultrasonography, and MRI) and subsequently had surgery at our institution between January 2009 and December 2012. Of these patients, 185 patients were diagnosed with T1-T2 invasive breast cancer and axillary lymph node metastases. The patients were excluded if they had received neoadjuvant chemotherapy (n=14) or underwent excision biopsy (n=8), and consequently, a total of 163 patients were included in this study.

The patients' medical records were reviewed to identify the clinical symptoms (*e.g.* the presence of a palpable mass). The pathological reports were also reviewed to determine the tumor size, histological grade, hormone receptor status [estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2)] and presence of nodal metastases. The ER, PR, and HER2 statuses were determined by immunohistochemical analysis. The final nodal status was determined by reviewing surgical and pathological reports according to the current American Joint Committee on Cancer recommendations. All patients with positive findings at sentinel node biopsy underwent axillary dissection.

Imaging analysis. Mammography was performed using a Selenia system (Lorad, Bedford, CT, USA). Standard two-view mammography (mediolateral, oblique and craniocaudal) was performed with additional views as necessary. Breast US was performed using a 5-12 MHz linear transducer with an IU-22 (Philips Medical Systems, Best, the Netherlands). Breast MRIs were performed after mammography and US and were available for all patients. The MRI examinations were performed using a 3.0 T MRI system (Signa HDxt; General Electric Medical Systems, Milwaukee, WI, USA) with a dedicated 8-channel breast coil. After obtaining a transverse localizer image, sagittal fat-suppressed T2-weighted fast spin-echo images were obtained. Dynamic contrast-enhanced MRI examinations included one pre-contrast and five post-contrast, sagittal image acquisitions using a fat-suppressed T1-weighted 3D fast spoiled gradient-recalled echo sequence with parallel volume imaging. Delayed contrast-enhanced 3D fast spoiled gradient-echo images with fat suppression in the axial plane were also obtained. Gadoterate meglumine (Dotarem; Guerbet, Aulnay-Sous-Bois, France) was injected into the ante-cubital vein using an automated injector (Spectris Solaris, Medrad Europe, Maastricht, the Netherlands) at a dose of 0.1 mmol per kilogram of body weight and at a rate of 3 ml/s followed by a 20-ml saline flush.

Two breast imaging radiologists with 5 and 9 years of experience (M.Y.K and N.C), respectively, in interpreting all three techniques, independently reviewed the mammography, US, and MRI studies in a blinded fashion. In cases with discrepant results, a final consensus was reached after discussion. The images were interpreted using the morphological criteria described for mammography, ultrasonography, and MRI in the American College of Radiology's BI-RADS lexicon (11). Lesion features were described on a per-patient basis, even if there were multiple tumors in one patient because the TNM system uses only the index lesion in staging women with multiple cancer in one breast. For identification of positive lymph nodes, US morphological criteria were used as

Table I. *Patients and disease characteristics*.

	pN1 (n=116)	pN2/3 (n=47)	*p*-Value
Mean age (years)±SD	50.5±11.2	48.3±10.1	0.230
Tumor size (cm)	2.32±0.91	2.81±1.08	0.003
T Stage			0.032
T1	48 (41.4)	11 (23.4)	
T2	68 (58.6)	36 (76.6)	
Symptom			0.336
Asymptomatic	27 (23.3)	9 (19.1)	
Palpable	79 (68.1)	31 (66.0)	
Bloody nipple discharge	2 (1.7)	0 (0)	
Mastalgia	7 (6.0)	7 (14.9)	
Other	1 (0.9)	0 (0)	
Operation type			0.058
Breast-conserving surgery	71 (61.2)	21 (44.7)	
Mastectomy	45 (38.8)	26 (55.3)	
Pathology			0.500
IDC	13 (11.2)	3 (6.4)	
IDC with DCIS	97 (83.6)	40 (85.1)	
IDC with mucinous cancer	2 (1.7)	1 (2.1)	
ILC with LCIS	4 (3.4)	2 (4.3)	
ILC	0 (0)	1 (2.1)	
Multifocality or Multicentricity			1.000
Negative	83 (71.6)	34 (72.3)	
Positive	33 (28.4)	13 (27.7)	
Histological grade			0.002
1	26 (22.4)	0 (0.0)	
2	53 (45.7)	23 (48.9)	
3	36 (31.0)	24 (51.1)	
Unknown	1 (0.9)	0 (0.0)	
Lymphovascular invasion			0.009
Negative	71 (61.2)	18 (38.3)	
Positive	45 (38.8)	29 (61.7)	
Estrogen Receptor			0.553
Negative	28 (24.1)	14 (29.8)	
Positive	88 (75.9)	33 (70.2)	
Progesterone receptor			0.387
Negative	54 (46.6)	26 (55.3)	
Positive	62 (53.4)	21 (44.7)	
HER2			0.876
Negative	86 (74.1)	33 (70.2)	
Positive	28 (24.1)	13 (27.7)	
Unknown	2 (1.7)	1 (2.1)	
Triple negative	18 (15.5)	9 (19.1)	0.572

Data are the numbers of patients, with percentages in parentheses. IDC: Invasive ductal carcinoma, DCIS: ductal carcinoma *in situ*, ILC: invasive lobular carcinoma, LCIS: lobular carcinoma *in situ*.

Table II. *Mammographic findings of pN1 and pN2 or higher nodal disease.*

	pN1 (n=116)	pN2/3 (n=47)	*p*-Value
Mammographic finding			0.479
Normal	8 (6.9)	4 (8.5)	
Masses	58 (50)	19 (40.4)	
Masses with calcifications	21 (18.1)	14 (29.8)	
Focal asymmetry	11 (9.5)	2 (4.3)	
Focal asymmetry with calcifications	12 (10.3)	5 (10.6)	
Calcifications only	4 (3.4)	3 (6.4)	
Architectural distortion	2 (1.7)	0 (0)	
Mass			
Total	79	33	
Shape			0.988
Oval	3 (3.8)	1 (3.0)	
Round	2 (2.5)	1 (3.0)	
Lobular	16 (20.3)	6 (18.2)	
Irregular	58 (73.4)	25 (75.8)	
Margin			0.665
Circumscribed	4 (5.1)	0 (0)	
Microlobulated	6 (7.6)	3 (9.1)	
Obscured	6 (7.6)	4 (12.1)	
Indistinct	29 (36.7)	13 (39.4)	
Spiculated	34 (43.0)	13 (39.4)	
Density			0.510
Hyperdense	51 (64.6)	24 (72.7)	
Isodense	28 (35.4)	9 (27.3)	
Calcifications			0.023
Total	37	22	
Fine linear or pleomorphic	21 (56.8)	19 (86.4)	
Punctate or amorphous	16 (43.2)	3 (13.6)	

Data are the numbers of patients, with percentages in parentheses.

Table III. *Ultrasonographic findings of pN1 and pN2 or higher nodal disease.*

	pN1 (n=116)	pN2/3 (n=47)	*p*-Value
Ultrasonographic finding			0.656
Mass only	100 (86.2)	39 (83.0)	
Mass with calcifications	15 (12.9)	8 (17.0)	
Calcifications only	1 (0.9)	0 (0.0)	
Mass			
Total	115	47	
Shape			0.496
Oval	22 (19.1)	6 (12.8)	
Round	1 (0.9)	0 (0.0)	
Irregular	92 (80.0)	41 (87.2)	
Margin			0.410
Circumscribed	2 (1.7)	1 (2.1)	
Indistinct	17 (14.8)	4 (8.5)	
Angular	5 (4.3)	5 (10.6)	
Microlobulated	59 (51.3)	27 (57.4)	
Spiculated	32 (27.8)	10 (21.3)	
Orientation			0.008
Parallel	87 (75.7)	44 (93.6)	
Nonparallel	28 (24.3)	3 (6.4)	
Echogenicity			0.433
Complex	3 (2.6)	0 (0)	
Hypoechoic	111 (96.5)	47 (100)	
Isoechoic	1 (0.9)	0 (0)	

Data are the numbers of patients, with percentages in parentheses.

follows: diffuse cortical thickening; focal cortical mass and/or thickening; effacement or replacement of the fatty hilum (2). Lymph nodes that did not meet these criteria were considered as negative for metastasis.

Statistical analysis. The clinical, mammographic, US and MRI features were compared between pN1 and pN2 or higher disease stages using the chi-square or Fisher's exact tests for categorical variables and Student's *t*-test for continuous variables. The sensitivity of US in detecting positive lymph nodes was obtained. All statistical analyses were carried out using SPSS version 17.0 for Windows (SPSS, Chicago, IL, USA). The results were considered significant at *p*-values<0.05.

Results

Patients and disease characteristics. Of the 163 T1-T2 breast carcinomas cases with nodal metastases, 116 (71.2%) were of pN1 metastatic disease and 47 (28.8%) were of pN2 or higher metastatic disease (Table I). The mean invasive tumor size was 2.3 cm (range=0.1-5.0 cm) for pN1 disease and 2.8 cm (range=0.2-4.5 cm) for pN2 or higher disease. Invasive tumor sizes larger than 2 cm were more common in pN2 or higher disease than in pN1 disease (p=0.032). Compared to patients with pN1 disease, patients with pN2 or higher disease had higher histological grades (p=0.002) with lymphovascular invasion (p=0.009). There were no significant differences in patient symptoms (p=0.336), operation type (p=0.058), pathology type (p=0.500), multi-focality or multi-centricity (p=1.000) or hormone receptor status according to nodal status.

Mammographic findings. Mammographic findings of T1-T2 cancer with nodal metastasis are listed in Table II. Out of the T1-T2 cases that had masses on mammography, there were no significant differences in the shape (p=0.988), margin (p=0.665) or density (p=0.510) between pN1 and pN2 or higher disease. There was a significant association between the presence of calcifications and nodal status (p=0.023). Overall, 37 (31.9%) mammograms of patients with pN1 disease and 22 (46.8%) of patients with pN2 or higher disease showed calcifications. Twenty-one (56.8%) out of 37 patients who had pN1 disease with calcifications and 19 (86.4%) out of 22 patients who had pN2 or higher disease with calcifications had fine linear or pleomorphic calcifications.

Table IV. *Magnetic resonance imaging MRI findings of pN1 and pN2 or higher nodal disease*

	pN1 (n=116)	pN2/3 (n=47)	*p*-Value
Lesion type			0.766
Mass with/without non-mass	106 (91.4)	42 (89.4)	
Non-mass	10 (8.6)	5 (10.6)	
Mass			
Shape			0.533
Oval	3 (2.8)	0 (0)	
Lobulated	52 (49.1)	22 (52.4)	
Irregular	51 (48.1)	20 (47.6)	
Margin			0.802
Smooth	5 (4.7)	1 (2.4)	
Irregular	75 (70.8)	30 (71.4)	
Spiculated	26 (24.5)	11 (26.2)	
Internal enhancement			0.308
Homogenous	1 (0.9)	0 (0.0)	
Heterogeneous	76 (71.7)	35 (83.3)	
Rim enhancement	29 (27.4)	7 (16.7)	
Kinetics			1.000
Delayed or plateau	5 (4.7)	2 (4.8)	
Washout	101 (95.3)	40 (95.2)	
Non-mass			
Distribution			0.256
Focal	1 (10.0)	0 (0.0	
Segmental	6 (60.0)	5 (100.0)	
Regional	3 (30.0)	0 (0.0)	
Internal enhancement			0.497
Homogenous	1 (10.0)	0 (0.0	
Heterogeneous	5 (50.0)	4 (80.0)	
Clumped	4 (40.0)	1 (20.0)	
Kinetics			1.000
Washout	9 (90.0)	5 (100.0)	
Delayed or plateau	1 (10.0)	0 (0.0)	

Data are the numbers of patients, with percentages in parentheses.

US findings. US revealed masses in all patients except for one with pN1 disease whose sonogram showed calcifications without any associated masses (Table III). Out of the T1-T2 carcinomas that appeared as masses on US, there were significant differences in the appearance or orientation between pN1 and pN2 or higher disease. pN1 disease was more likely to have non-parallel orientation than pN2 or higher disease (p=0.008). Other US features, such as shape (p=0.496), margin (p=0.410) and echogenicity (p=0.433), were not associated with nodal status.

Out of the 163 cases, 84 (51.5%) US examinations detected suspicious lymph nodes and 79 (48.5%) did not detect any abnormality in the axilla on US. According to T stage, the sensitivity of US was 35.6% (21 of 59) in T1 cancer, and 60.6% (63 of 104) in T2 cancer.

Dynamic contrast-enhanced MRI findings. Upon MRI, there was no significant difference in lesion type (p=0.766) between pN1 and pN2 or higher disease (Table IV). Among the T1-T2 cases that showed mass-like enhancement on MRI, we did not observed a significant difference between nodal status and lesion shape (p=0.533), lesion margin (p=0.802), internal enhancement (p=0.308) and kinetics (p=1.000). We also did not observe any significant difference between nodal status and lesion distribution (p=0.256), internal enhancement (p=0.497) and kinetics (p=1.000) in the T1-T2 carcinomas exhibiting non-mass-like enhancements on MRI.

Discussion

It is important to make the distinction between pN1 and pN2 or higher metastatic disease in preoperative axillary lymph node evaluations because a complete axillary dissection may not be beneficial in nodal staging or prognosis of patients with minimal pN1 disease (12). According to the American College of Surgeons Oncology Group Z0011 Trial, there was no survival benefit or reduction in local recurrence in patients with only one or two metastatic lymph nodes who underwent sentinel node biopsy *versus* those who underwent sentinel axillary lymph node dissection (12). The results of this trial could promote a trend towards omitting completion axillary dissection when only a few metastatic lymph nodes are observed on a sentinel node biopsy; this is particularly true for patients who are expected to be at low risk for nodal metastasis, such as patients with small breast tumors (3). However, pN2 or higher metastatic disease is considered to be a locally-advanced disease and requires for adequate adjuvant treatment. In addition, Fraile *et al*. reported that 1-15% of patients with negative sentinel node biopsies actually had other metastatic lymph nodes in the same axillary region (6).

In the present study, we were able to demonstrate a significant association between some imaging features and the extent of nodal disease in patients with T1-T2 breast cancer with nodal metastases. On mammography, primary tumors with pN2 or higher disease are more likely to show pleomorphic or linear-branching micro-calcifications than those with pN1 disease (p=0.023). The association between mammographic calcifications and tumor attributes or prognosis has been previously demonstrated (13). The fine, linear-branching calcifications, known as casting-type calcifications, result from extensive tumor necrosis and are often associated with high grade ductal carcinoma *in situ* of comedo-type cancer (14). High-grade ductal carcinoma *in situ* with or without an invasive cancer is known to be associated with a poor prognosis (15, 16). In a prior study of 1-14 mm invasive breast carcinomas and their mammographic appearance, Tabar *et al*. found that casting-type calcifications have some predictive value for lymph node positivity, but there has been no study investigating the association between mammographic calcifications and the extent of nodal disease (17).

On ultrasonography, primary tumors with pN1 disease were more likely to have non-parallel orientation than those with pN2 or higher disease (p=0.008); 24.3% (28 out of 116) of primary tumors with pN1 disease were taller than wide, while 6.4% (3 out of 47) of those with pN2 or higher disease were. This result may be explained by the significantly different primary tumor sizes between patients with pN1 disease and those with pN2 or higher disease. In our study, primary tumors with pN1 disease were more likely to be T1 cancer (41.4%, 48 out of 116) compared to those with pN2 or higher disease (23.4%, 11 out of 47). Carcinomas that are taller than wide are primarily small lesions and mostly arise from the anterior lobules of the lobar duct system histologically; however, as the tumor enlarges and grows into the main ductal system, its growth pattern has a tendency to become wider rather than taller (18).

This study has limitations. Its main limitations are the small sample size and its retrospective design. In addition, we did not make a distinction between T1 and T2 cancer; therefore, our results need further confirmation in a data set that is large enough to perform a sub-group analysis according to T stage.

In conclusion, on mammography, T1-T2 breast carcinomas with pN2 or higher metastatic disease are more likely to present with pleomorphic or linear-branching calcifications. On ultrasound, T1-T2 carcinomas with pN2 or higher disease are more likely to have a non-parallel orientation. Being familiar with the imaging features of T1-T2 breast cancer with nodal metastasis may be helpful in preoperatively evaluating the extent of nodal disease.

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