Significance of Lymphatic Invasion Combined with Size of Primary Tumor for Predicting Sentinel Lymph Node Metastasis in Patients with Breast Cancer

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Abstract. *Background/Aim: Lymphatic invasion (ly) may mainly reflect the selective affinity of breast cancer cells for lymph nodes. We conducted the present study to investigate whether the presence of lymphatic invasion is a predictor of sentinel lymph node (SLN) metastasis in clinically node-negative breast cancer. Patients and Methods: We retrospectively evaluated the cases of 202 consecutive female patients with clinically node-negative primary breast cancer who underwent a radical breast operation with SLN biopsy. We examined the relationship between SLN metastasis and the significance of clinicopathological factors, including lymphatic invasion. Results: Among the 202 patients, 49 (24.3%) had SLN metastasis. The univariate and multivariate analyses revealed that the size of the tumor and lymphatic invasion were independent risk factors for SLN metastasis. Among the 96 patients who were ly-negative and had a tumor size of less than 20 mm, only 5 (5.2%) had 1-2 metastases within the SLN. Among the 34 patients who were ly-negative and had a tumor size of less than 10 mm, there were no patients with SLN metastasis. Conclusion: Our results suggest that the presence of lymphatic invasion combined with the size of the primary cancer could be considered a strong risk factor for SLN metastasis in clinically node-negative breast cancer, and patients with a tumor size of less than 20 mm and clinically node-negative breast cancer may avoid axillary lymph node dissection after SLN biopsy. There is also a possibility that SLN biopsy could be unnecessary for patients with clinically node-negative breast cancer who are ly-negative and have a tumor size of less than 10 mm.*

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Sentinel lymph node (SLN) biopsy was developed as a minimally invasive operative procedure to precisely determine the presence of axillary lymph node metastases in patients with clinically negative nodes (1-5). Although the majority of patients with breast cancer have clinically-negative axillary nodes at preoperative assessment, around 15-20% of these women will have metastatic disease within the lymph nodes based on the operative SLN biopsy (6). It may be possible to avoid unnecessary axillary lymph node dissection, including SLN biopsy, in selected patients. The recent results of the American College of Surgeons Oncology Group Z0011 trial suggested that some women would be safe from recurrence without further axillary treatment if they have fewer than three involved SLN with no extracapsular spread (6). We previously demonstrated that extracapsular invasion (ECI) at a metastatic SLN was significantly associated with the presence of disease-positive non-sentinel lymph nodes in patients with breast cancer (5). The mechanism or process of metastatic spread of tumor cells to axillary lymph nodes in patients with breast cancer is not fully understood; however, ECI may be a key process following distant lymph node metastasis (5, 7-9). The ability of metastatic nodes to recruit degradation factors that permit cancer cells to break through the lymph node capsule is an important process in lymphatic spread (5, 7-11). ECI is thought to be a mechanism of 'node-to-node expansion' as locoregional lymphatic progression (5, 7-9). In other words, with regard to SLN metastasis, it may be that in order to spread to lymph nodes from the primary tumor, tumor cells must invade the lymphatic vessels (*i.e.* lymphatic invasion of the primary tumor). Invasion of the lymphatic vessels by the tumor cells enables the tumor cells to penetrate into the lymphatic system. Both experimental tumor models and human clinicopathological data indicate that the growth of lymphatic vessels near solid tumors is

often associated with lymph node metastasis (9-13). The presence of lymphatic invasion in breast cancer could be a potential indicator of the ability of breast cancer cells to metastasize to lymph nodes.

In the present study, we retrospectively investigated the relationship between lymphatic invasion and SLN metastasis in patients with clinically node-negative breast cancer who underwent SLN biopsy. We addressed whether it is possible to avoid SLN biopsy, as well as axillary lymph node dissection.

Patients and Methods

We retrospectively investigated the cases of 202 consecutive patients with clinically node-negative primary breast cancer who underwent radical breast surgery with SLN biopsy at the Department of General Surgical Science, Gunma University Hospital, from January 2010 to November 2014. Patients with previously diagnosed breast cancer or incomplete clinical information were excluded, and male patients were excluded. None of the patients had received preoperative chemotherapy. The resected margins were all clear. Informed consent was obtained from all patients.

The details extracted from the database were age, histological type, primary tumor size, nuclear grade, lymph node metastasis, lymphatic invasion (ly), vascular invasion (v), estrogen (ER) or progesterone (PgR) status, and human epidermal growth factor receptor 2 (HER2) score of the primary tumor. The ER and PgR status were assessed using ALLRED scores, and an ALLRED score of 3 or higher was defined as ER- or PgR-positive (14). None of the patients died of surgical complications.

Statistical analysis. The breast cancer cases were divided into two groups on the basis of the presence or absence of SLN metastasis. We conducted a univariate statistical analysis using Fisher's exact test or the χ^2 test with or without Yates' correction. To compare the two groups, we used Student's *t*-test. To test the independence of the risk factors, we entered the variables into a multivariate logistic regression model. Differences were considered significant when $p<0.05$.

Results

We divided the cases with clinically node-negative breast cancer into two groups based on the presence or absence of SLN metastasis. Among the 202 patients, 49 (24.3%) had SLN metastasis. Table I summarizes not only the patient characteristics but also the results of the univariate analysis conducted to determine the relationship between the clinicopathological variables and SLN metastasis. The univariate analysis revealed that the size of the tumor and lymphatic invasion were statistically significant. The multivariate analysis also revealed that greater tumor size (HR 4.791; 95% CI 2.418-9.494, $p=0.003$), which may reflect invasive disease, and lymphatic invasion (HR 8.381; 95%CI 4.023-17.436, $p<0.001$), which may reflect lymphatic disease, were independent risk factor for SLN metastasis. In the ly-positive group, there were 36 patients (48.6%) with SLN metastases, and in the ly-negative group, there were 13 patients (10.2%) with SLN metastases. Among the 96 patients in the group with ly-negative disease and a tumor size of less than 20 mm, only five (5.2%) had SLN metastases. Furthermore, there were only one or two lymph node metastases within the SLN in each of these five cases without any non-SLN metastasis. Among the 34 patients with ly-negative disease and tumor size less than 10 mm, there were no patients with SLN metastasis.

Discussion

The invasion of lymphatic vessels or blood vessels by tumor cells is the step of tumor cell dissemination and metastasis that is most critical for predicting disease recurrence or prognosis. The routine assessment of lymphovascular invasion is now part of the minimum dataset in reporting of breast cancer pathology (15). However, in many previous studies, the term lymphovascular invasion included both vascular and lymphatic invasion (15-17). As described above, tumor cells invade the lymphatic vessels, and this enables them to penetrate into the lymphatic system. Lymphatic invasion may mainly reflect the selective affinity of breast cancer cells for lymph nodes (10, 11). We conducted the present study to investigate whether the presence of lymphatic invasion, reflecting lymphatic spread, is a predictor of SLN metastasis in clinically node-negative breast cancer. The key observations made in this study can be summarized as follows: (i) the presence of lymphatic invasion and greater tumor size were independent risk factors for SLN metastasis; and (ii) among the group of patients without lymphatic invasion and tumor size <20 mm, only 5.2% had only two or fewer metastases within the SLN, and those with tumor size <10 mm had no SLN metastases. These results suggest that the presence of lymphatic invasion combined with the size of the primary cancer could be considered a strong risk factor for SLN metastasis in breast cancer, and patients with a tumor size of less than 20 mm and clinically node-negative breast cancer may avoid axillary lymph node dissection after SLN biopsy. There is also a possibility that SLN biopsy may be unnecessary in patients with clinically node-negative ly-negative breast cancer who and with tumor size of less than 10 mm. This possibility should be investigated in further studies.

Lymphovascular invasion has been reported as a prognostic factor in patients with breast cancer (15-17). The invasion of blood vessels, not lymphatic vessels, by tumor cells is the critical step in tumor cell dissemination and metastasis for predicting disease recurrence or prognosis (10-11). We previously demonstrated that the presence of vascular invasion, but not lymphatic invasion, could be a strong prognostic factor for breast cancer (10). Lymphatic invasion may mainly represent the selective affinity of breast

Table I. *Patients' characteristics and clinicopathological features associated with sentinel lymph node metastasis.*

Characteristic		Sentinel lymph node metastasis		*p*-Value
		Negative n=153	Positive n=49	
Age (years)*		58.8±12.2	56.9±11.8	0.877
Histrogical type (n)	Invasive ductal carcinoma	127	40	0.104
	Invasive lobular carcinoma	7	6	0.877
	Other	18	3	
Tumor size (mm)*		17.5±12.8	28.5±20.1	<0.001
ER-positive (n)		123	42	0.351
PR-positive (n)		109	39	0.335
HER2-positive (n)		26	9	0.997
Lymphatic invasion-positive (n)		38	36	<0.001
Vascular invasion-positive (n)		16	10	0.118
Nuclear grade 3 (n)		48	20	0.297

*Mean±SD. ER: Estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor-2.

cancer cells for lymph nodes (10, 11). Many previous studies have demonstrated the relationship between lymphatic invasion and lymph node metastasis (18, 19) and our results are consistent with those studies.

Tumor size was associated with lymphatic invasion, which may reflect lymphatic spread. In the current study, there were slight linear associations between the size of the tumor and lymphatic invasion when Pearson's correlation was used (r=0.244, $p<0.001$). However, lymphatic invasion and the size of the tumor are independent variables in our study; the utility of tumor size as an additional useful risk factor had been investigated. From these findings, to predict SLN metastasis among patients without lymphatic invasion, it is meaningful to determine the subset of patients with a tumor size of less than 20 mm (T1).

This study has several potential limitations. The major limitation is that it used retrospective methods of data collection. In addition, the number of cases was relatively small. However, the clinical implications of the data we obtained are very important. Additional research is required to explore the significance of lymphatic invasion combined with the size of the tumor in predicting SLN metastasis in patients with clinically node-negative breast cancer.

In conclusion, our present findings suggest that the presence of lymphatic invasion combined with the size of the primary cancer could be considered a strong risk factor for SLN metastasis in clinically node-negative breast cancer. Patients with a tumor size of less than 20 mm and clinically node-negative breast cancer undergoing SLN biopsy may avoid axillary lymph node dissection. There is also a possibility that SLN biopsy may be unnecessary in patients with clinically node-negative breast cancer that is ly-negative and has a tumor size of less than 10 mm. Analyses of large randomized trials are warranted to evaluate the relationship between the combination of the two factors investigated here and SLN metastasis in patients with clinically node-negative breast cancer.

Competing Interest Statement

The Authors declare that they have no competing financial interests in regard to this study.

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