Impact of the Prognostic Value of Vascular Invasion, but Not Lymphatic Invasion, of the Primary Tumor in Patients with Breast Cancer

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Abstract. *Background: The prognostic value of lympho-vascular invasion (LVI) in patients with breast cancer is unclear. Lymphatic invasion may mainly represent the selective affinity of breast cancer cells for lymph nodes. This study was undertaken to evaluate the presence of vascular invasion that may reflect systemic disease as a predictor of disease recurrence in breast cancer, separate from lymphatic invasion of the primary tumor. Patients and Methods: We retrospectively evaluated the cases of 263 consecutive female patients with primary breast cancer who underwent a radical breast operation. We examined the relationship between recurrence and the prognostic significance of clinico-pathological factors, particularly lymphatic (Iy) and vascular invasion (v). Results: The presence of lymphatic invasion and that of vascular invasion were significant in univariate analysis. The presence of vascular invasion was an independent prognostic factor, but lymphatic invasion lost its prognostic significance in multivariate analysis. Among the 91 patients in the ly−/v− group, 5 (5.5%) had disease recurrence, and among the 73 patients in the ly+/v− group, 5 (6.8%) had disease recurrence. On the other hand, among the 95 patients in the ly+/v+ group, 19 (20.0%) had a recurrence, and among the 3 patients in the ly-/v+ group, one had a recurrence. It is interesting to note that despite the presence of lymphatic invasion, the group without vascular invasion (ly+/v−) had a few patients with distant metastases, a result which is similar to that of the ly−/v− group.*

Conclusion: The presence of vascular invasion, but not lymphatic invasion, could be an indicator of high biological aggressiveness and may be a valid prognostic factor for breast cancer.

A correct definition of poor prognostic factors for breast cancer may help guiding more aggressive adjuvant treatment protocols. The prognostic significance of lymphovascular invasion (LVI) in breast cancer has been investigated (1-10), and the routine assessment of LVI is now part of the minimum data set for breast cancer pathology reporting (1). However, LVI is not incorporated into most of the internationally-recognized staging systems (1). Some studies have demonstrated a clear relation between LVI and cancer outcome, but other studies have demonstrated controversial results (8-10). The prognostic significance of LVI remains unclear.

Tumor cells invade lymphatic vessels, and this invasion enables 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 (11-13). 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. Lymphatic invasion may represent mainly the selective affinity of breast cancer cells for lymph nodes.

However, the phenomenon in which tumor cells invade blood vessels, not lymphatic vessels, is the critical step of tumor cell dissemination and metastasis for predicting disease recurrence or prognosis. Vascular invasion of the primary tumor may, thus, reflect systemic disease. We, therefore, hypothesized that vascular invasion of the primary tumor would more greatly affect the risk of recurrent disease and prognosis compared to lymphatic invasion. In the present study, we retrospectively investigated the relationship between vascular invasion with and without lymphatic invasion and recurrence in patients with operable breast cancer.

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Patients and Methods

We retrospectively investigated the cases of 263 consecutive patients with primary breast cancer who underwent radical breast operation at the Gunma Cancer Center from 1994 to 1995 or at the Department of General Surgical Science, Gunma University Hospital, from January 1996 to December 2012. Patients with previously-diagnosed breast cancer or incomplete clinical information were excluded, and male patients were excluded as well. None of the patients had received preoperative chemotherapy. The resected margins were all clear of tumor. Informed consent was obtained from all patients.

Details extracted from the database were age, histological type, primary tumor size, nuclear grade, lymph node metastasis, lymphatic or vascular invasion, estrogen (ER) or progesterone (PgR) status and human epidermal growth factor receptor-2 (HER2) score of the primary tumor. The ER and PgR status was assessed by Allred scores (14, 15), and an Allred score of 3 or higher was defined as ER- and PgR-positive. The overall median follow-up period was 7.46 years, and 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 recurrence. 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 were into a multivariate logistic regression model with a likelihood of $p<0.05$. The relapse-free survival (RFS) and overall survival (OS) were calculated using the Kaplan−Meier method. The log-rank test was used to evaluate differences between the overall survival and the recurrence-free interval. Differences were considered significant when $p<0.05$.

Results

Vascular invasion is the factor associated with disease recurrence in breast cancer. We divided the cases with breast cancer into two groups based on the presence of recurrence. Among the 263 patients, 30 (11.4%) had recurrent disease. Table I summarizes not only patient characteristics but also the results of the univariate analysis conducted to determine the relationship between the clinicopathological variables and recurrent disease. The univariate analysis revealed that lymph node metastasis, the expression of PgR, lymphatic invasion, and vascular invasion were statisticaly significant. The multivariate analyses revealed that only vascular invasion ($p=0.004$) was an independent negative prognostic factor. Lymphatic invasion ($p=0.923$), lymph node metastasis ($p=0.550$) and PgR ($p=0.073$) lost their significance in the multivariate analysis. Because lymphatic invasion was associated with vascular invasion in our study (the Spearman correlation coefficient was 0.510; $p<0.001$), lymphatic invasion lost its significance in the multivariate analysis.

The RFS shown by the Kaplan−Meier curves was significantly shorter for the patients with vascular invasion ($p=0.009$) (Figure 1a). In addition, the OS revealed by the Kaplan−Meier curves was significantly shorter for patients with vascular invasion ($p=0.039$) (Figure 1b). The two types

Table I. *Patients' characteristics and clinicopathological features associated with recurrent disease.*

	Recurrence		
	Negative N=233	Positive N=30	*p*-Value
Age (years)*	55.9±12.3	52.3±11.0	0.137
Tumor size >20 mm (n)	120	19	0.222
Lymph node metastasis-positive (n)	98	19	0.027
Histrogical type (n)			
Invasive ductal carcinoma	203	27	0.877
Others	30	3	
Estrogen receptor status (positive, n)	177	18	0.060
Progesteron receptor status (positive, n)	126	10	0.032
HER2 status (positive, n)	33	5	0.927
Lymphatic invasion (positive, n)	144	24	0.923
Vascular invasion (positive, n)	78	20	<0.001
Nuclear grade 3 (n)	53	8	0.632

*Mean±SD.

of survival curves indicate a significantly lower rate of survival among the patients with vascular invasion. On the other hand, the RFS by the Kaplan−Meier curves was shorter for patients with lymphatic invasion ($p=0.013$), however, the OS by the Kaplan−Meier curves did not differ among patients with lymphatic invasion ($p=0.507$) (Figure 2).

Lymphatic invasion without vascular invasion does not affect the risk of recurrent disease or prognosis. We found that the presence of vascular invasion (v+), which may reflect systemic disease, was an independent risk factor of recurrent disease. Conversely, our results did not show that lymphatic invasion (ly+) was of independent prognostic value in RFS and OS. Among the 91 patients in the ly−/v− group, 5 (5.5%) had disease recurrence, and among the 73 patients in the ly+/v− group, 5 (6.8%) had disease recurrence. On the other hand, among the 95 patients of the ly+/v+ group, 19 (20.0%) had a recurrence, and among the 3 patients in the ly−/v+ group, 1 had a recurrence. The RFS curves for the various groups, based on lymphatic invasion and vascular invasion of the primary tumor, are shown in Figure 3. The RFS curve for the ly+/v− group was almost the same as that for the ly−/v− group.

Discussion

Routine assessment of LVI is now part of the minimum dataset for breast cancer pathology reports (1). The prognostic significance of LVI in breast cancer has been investigated, but the prognostic value of LVI is unclear and its prognostic value in patients with breast cancer is controversial (1-10). The use of LVI in clinical management decisions thus remains a matter
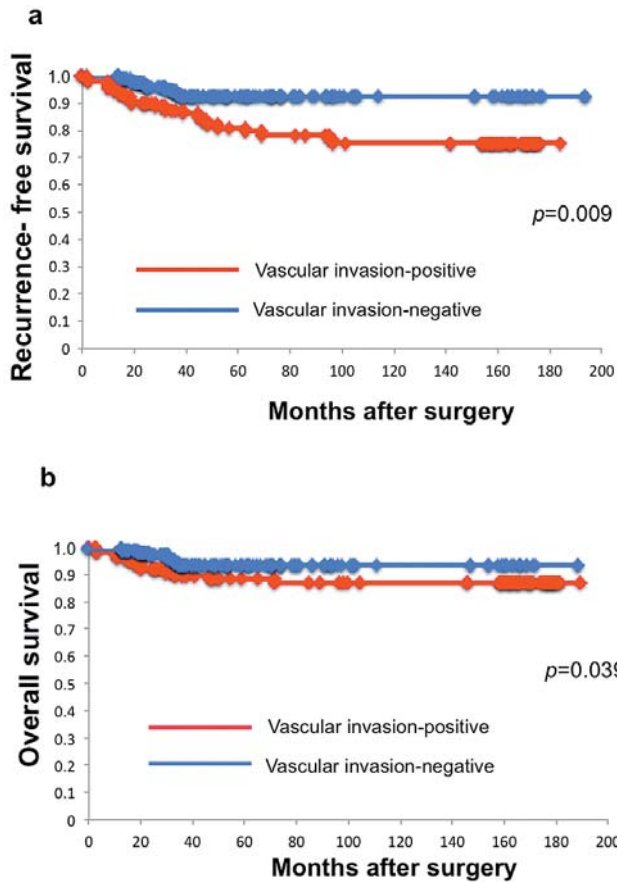
Figure 1. *The time-to-tumor recurrence (RFS) and overall survival (OS) by Kaplan−Meier curves differed among breast cancer patients with presence of vascular invasion in the primary tumor. With a median follow-up duration of 59.0 months for RFS and 74.0 months for OS, both survival curves suggest a significantly lower rate of survival among patients with vascular invasion.*

Figure 2. *The time-to-tumor recurrence by the Kaplan−Meier curves differed among patients with breast cancer with presence of lymphatic invasion in the primary tumor, but overall survival curves did not differ among patients with lymphatic invasion.*

	Recurrence (%)
ly − / v −	5/91 (5.5%)
ly + / v −	5/73 (6.8%)
ly − / v +	1/3 (33.3%)
ly + / v +	19/76 (20.0%)

Figure 3. *Recurrence-free survival curves by vascular invasion (v) and lymphatic invasion (ly) of the primary tumor. The curve for the ly+/v− group was almost the same as that of the ly−/v− group.*

of debate. Tumor cell invasion of blood vessels or lymphatic vessels is the critical step of tumor cell dissemination and metastasis for predicting disease recurrence or prognosis. However, in many previous studies, LVI included both vascular invasion and lymphatic invasion (1-10).

As described above, tumor cells invade the lymphatic vessels, and this enables tumor cells to penetrate into the lymphatic system. Lymphatic invasion may thus reflect mainly the selective affinity of breast cancer cells for lymph nodes. We conducted the present study to investigate whether the presence of vascular invasion reflecting systemic disease is a predictor of disease recurrence in breast cancer, separate from lymphatic invasion of the primary tumor.

The key observations made in the present study can be summarized as follows: (i) the presence of lymphatic invasion and vascular invasion were significant in the univariate analysis; (ii) the presence of vascular invasion was
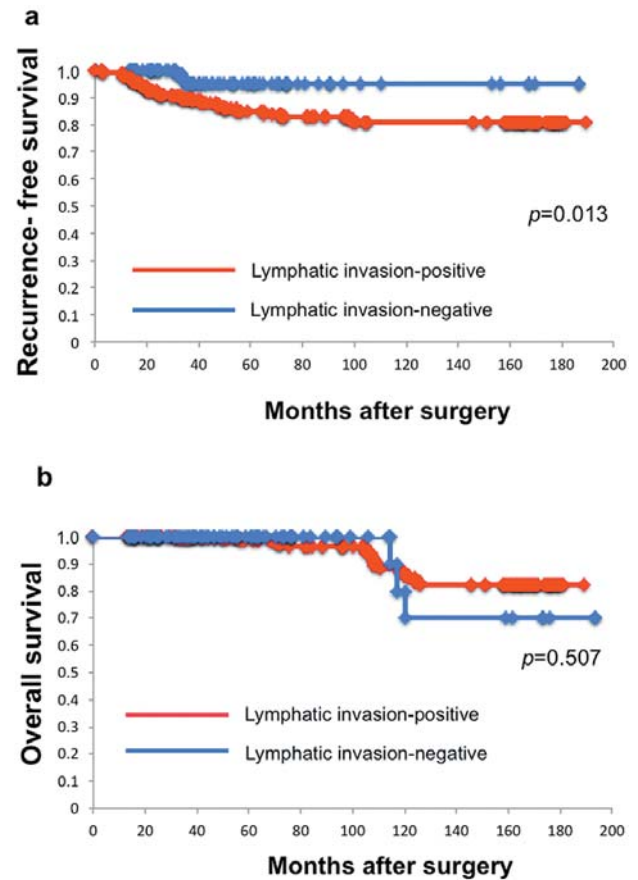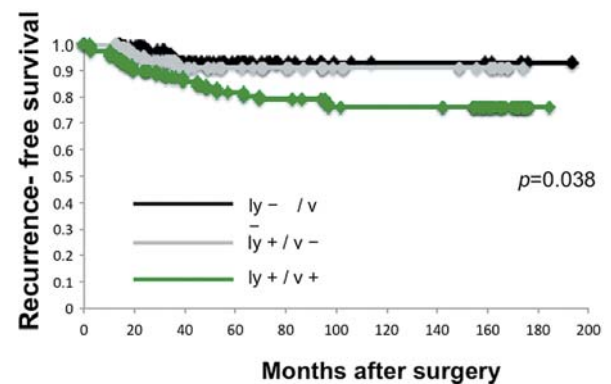
an independent prognostic factor, but lymphatic invasion lost its prognostic significance in the multivariate analysis; and (iii) most patients with distant metastases in our series had vascular invasion, which may reflect systemic disease, and the presence of lymphatic invasion without vascular invasion of the primary tumor did not affect the risk of recurrent disease. These results suggest that the presence of vascular invasion, but not lymphatic invasion, could be considered an indicator of high biological aggressiveness and may be a strong prognostic factor in breast cancer.

LVI has been reported as a prognostic factor in patients with breast cancer (1-10). In our study, a univariate analysis of the risk of recurrent disease by clinicopathological variables revealed that both lymphatic invasion and vascular invasion were statistically significant, but the multivariate analysis showed that only vascular invasion was an independent negative prognostic factor. The reason why lymphatic invasion lost its significance in the multivariate analysis is that lymphatic invasion was associated with vascular invasion, fact which may reflect systemic disease.

On the other hand, lymphatic invasion was related to lymph node metastasis. Many previous studies have demonstrated the relationship between lymphatic invasion and lymph node metastasis (16-18), and our results are consistent with those studies. Our previous study also demonstrated that galectin-3 expression is associated with vascular invasion (not lymphatic invasion) and metastasis, suggesting that galectin-3 plays a critical role in tumor progression in breast cancer *via* an invasive mechanism (19).

It is interesting to note that despite the presence of lymphatic invasion, the present study's patient group without vascular invasion (ly+/v−) had a few patients with distant metastases, similar to the ly−/v− group. Several previous studies suggested a relationship between LVI and prognosis (1-10), but those studies did not separate vascular invasion and lymphatic invasion. Because of the close association between vascular invasion and lymphatic invasion, vascular invasion may better represent systemic disease compared to lymphatic invasion. We, therefore, investigated the utility of vascular invasion as an additional useful prognostic indicator. We found that in order to predict systemic disease, it would be useful to identify the subset of patients with vascular invasion among breast cancer patients with or without lymphatic invasion.

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 vascular invasion in prognosis and in metastatic disease.

In conclusion, our present findings suggest that the presence of vascular invasion – and not that of lymphatic invasion – could be considered an indicator of high biological aggressiveness. Patients with vascular invasion may required for stronger adjuvant therapies because of the high risk of distant recurrence. Analyses from large randomized trials are warranted to evaluate the usefulness of vascular invasion as a prognostic factor.

Competing Interest Statement

The Authors declare that they have no competing financial interests.

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