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Non-Sentinel Lymph Node Metastasis is Hard to Predict by Clinicopathological Factors if SLN Metastasis in Two or Fewer Nodes in Breast Cancer

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Abstract

Background: The aim of this study was to investigate the association between sentinel lymph node (SLN) and/or non-SLN metastasis and clinicopathological factors in breast cancer.

Methods: We identified 176 invasive breast cancer patients by SLN biopsy (SLNB) and evaluated any association between clinicopathological factors and SLN and/or non-SLN metastasis.

Results: SLN metastasis was significantly associated with age (P = 0.0231), tumor size (P = 0.0039) and lymphovascular involvement (LVI) (P = 0.0002). Non-SLN metastasis was observed in 41.4% of cases. The involvement of more than three nodes was observed in more than 30% of cases with SLN metastasis in two or fewer nodes. There was no significant association between non-SLN metastasis and clinicopathological factors.

Conclusions: Non-SLN metastasis was apparent in more than 30% of cases even if SLN metastasis was present in two or fewer nodes but non-SLN metastasis was hard to predict by clinicopathological factors.

Keywords: Breast cancer; Sentinel lymph node; Non-sentinel lymph node; Metastasis

Introduction

In spite of new tumor markers have been widely studied, axillary lymph node metastasis remains a strong prognostic indicator for the patients with invasive breast cancer [1-3]. Axillary lymph node dissection (ALND) is the standard management approach for preoperatively-diagnosed node-positive breast cancer [4]. Since the 1990s, the introduction of sentinel lymph node (SLN) biopsy (SLNB) has resulted in changes in the management of the axilla [5]. SLNB for clinically N0 breast cancer and ALND for positive SLN have become the standard procedures.

Recent clinical trials have suggested that there is no difference in outcome between patients with positive SLN if they are treated with ALND or given no further axillary surgery [6, 7]. These studies raise doubts concerning the role of SLNB. A new trial compared SLNB with the assessment of whether an axillary ultra-sound is negative in patients with small breast cancer [8]. SLN metastasis has been observed in about 30% of SLNBs [9], so it is important to predict the axillary node status before SLNB. Various clinicopathological factors have been identified as independent predictors of axillary lymph node metastasis in early stage breast cancer [10]. These factors include clinical palpability [11-14], tumor size [11-17], lymphatic or vascular involvement [11-15, 17], tumor grade [11, 14], hormone receptor (HR) status [16, 17], age [12, 15, 16], and molecular subtype classification [3, 10, 18-26].

Predicting the non-SLN status is important because the ACOSOG Z0011 [6] and IBCSG 23-01 [7] studies both indicated that ALND should be avoided if SLN is positive. Analytical tools have been developed for predicting the risk of non-SLN metastasis following positive SLN [27-33] but these yield a false negative rate of 7-41% (ALND for < 10% risk of non-SLN metastasis) [34].

The aim of this study was to investigate: 1), the association between SLN metastasis and routinely-used clinicopathological factors; 2), the association between non-SLN metastasis and clinicopathological factors in breast cancer.

Materials and Methods

Patient selection

Patients with invasive breast cancer who received SNB at

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Table 1. Association Between SLN Metastasis and Clinicopathological Features (n = 176)

	Total	SLN		P value
		Negative (%)	Positive (%)	
Age				0.0231
≤ 50	59	44 (74.6)	15 (25.4)	
> 50	117	103 (88.0)	14 (12.0)	
Tumor size				0.0039
T1	138	122 (88.4)	16 (11.6)	
T2	32	21 (65.6)	11 (34.4)	
T3	6	4 (66.7)	2 (33.3)	
Histological grade				0.8171
I	122	103 (84.4)	19 (15.6)	
II	30	25 (83.3)	5 (16.7)	
III	24	19 (79.2)	5 (20.8)	
LVI				0.0002
Negative	163	141 (86.5)	22 (13.5)	
Positive	13	6 (46.2)	7 (53.8)	
ER and/or PR				0.4591
Negative	19	17 (89.5)	2 (10.5)	
Positive	157	130 (82.8)	27 (17.2)	
HER2				0.0859
Negative	122	98 (80.3)	24 (19.7)	
Positive	54	49 (90.7)	5 (9.3)	
Molecular subtypes				0.2965
Luminal A	72	56 (77.8)	16 (22.2)	
Luminal B	85	74 (87.1)	11 (12.9)	
HER2	6	6 (100)	0 (0)	
Triple negative	13	11 (84.6)	2 (15.4)	
Ki-67				0.3388
Ki-67 < 14%	95	77 (81.1)	18 (18.9)	
Ki-67 ≥ 14%	81	70 (86.4)	11 (13.6)	

SLN: sentinel lymph node; LVI: lymphovascular involvement; ER: estrogen receptor; PR: progesterone receptor.

Table 2. Multivariate Analysis of Clinicopathologic Factors

		P value	RR (95% CI)
Age	> 50 vs. ≤ 50	0.043	2.541 (1.029 - 6.274)
Tumor size	T1 vs T2, T3	0.004	4.066 (1.569 - 10.533)
LVI	(-)ve vs. (+)ve	0.015	4.924 (1.367 - 17.744)

RR: relative risk; CI: confidence interval; LVI: lymphovascular involvement.

Niigata University Hospital between January 2010 and December 2012 were enrolled into this study. ALND was performed in patients with macro- and micrometastasis in SLN, however, ALND was avoided in patients with isolated tumor cells in SLN. This study included a retrospective chart review. Patients with a complete data of clinicopathological factors including age, clinical and pathological tumor size, HR and HER2 status, and Ki-67 labeling index were enrolled (n = 176). These data of patients were analyzed following approval from the Institutional Review Board.

Pathological assessment

Immunohistochemical (IHC) ER and PR status was assessed and tumors were deemed positive for each receptor if at least 10% of the invasive tumor cells in a section exhibited nuclear staining. HER2 expression was examined by IHC, and a gene amplification assay using fluorescence in situ hybridization (FISH) was utilized in cases when it was difficult to decide the HER2 status by IHC. Ki-67 was also examined by IHC, and the results are expressed as the percentage of tumor cells stained by the antibody as described previously [35]. Hematoxylin eosin staining was used to assess lymphovascular involvement (LVI) as well as histological grading, which was defined according to Scarff-Bloom-Richardson system [36]. SLN metastasis was judged by intraoperative frozen section and was re-examined using fixed sections and re-judged postoperatively. The staging of breast cancer was defined by the TNM classification as proposed by the American Joint Committee on Cancer (AJCC). All of the IHC judgements were performed by several well-trained pathologists.

Patients were assigned into four subgroups, as proposed in the St Gallen International Expert Consensus [37], according to the results of their ER, PR, HER2 status and Ki-67 leveling index [38]. These groups were: the luminal A group with ER positive or PR positive, Her2 negative and Ki-67 < 14%; the luminal B group with ER positive or PR positive, Her2 positive or Ki-67 ≥ 14%; the HER2 group with ER negative, PR negative and Her2 positive; and the triple negative group with ER negative, PR negative and Her2 negative.

Statistical analysis

We examined the relationship between SLN metastasis and clinicopathological factors including ER and/or PgR status, Her2 status, subtype classification and Ki-67 expression. Univariate analysis was performed using the Chi-square test, and multivariate analysis was performed using the logistic regression model. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics and clinicopathological factors

A total of 176 patients were enrolled during the study period and all of these patients were female and 29 patients had SLN metastasis (16.5%). The mean age of the patients was 57.3 years old, and SLN metastasis was more frequent in younger patients (P = 0.0231). Tumor size was also associated with SN metastasis, and SLN metastasis was more frequent in larger tumors (P = 0.0039). LVI was also strongly associated with SLN metastasis (P = 0.0002) (Table 1). Multivariate analysis showed that age, tumor size and LVI were significant factors for predicting SLN metastasis (Table 2). The relative risk of younger age, large tumor size and prominent LVI was 2.541, 4.066 and 4.924, respectively. There was no significant correlation between SLN metastasis and ER and/or PgR status/Her2 status.

The percentage distribution of molecular subtypes among the 176 patients was as follows: luminal A in 40.9%; luminal B in 48.3%; HER2 in 3.4%; triple negative in 7.4%. There was no significant association between SLN metastasis and molecular subtype classification.

Table 3. Association Between SLN Metastasis and Non-SLN Metastasis (n = 29)

	Total	Number of non-SLN metastasis (%)				P value
		0	1	2	≥ 3	
SLN metastasis						0.1787
1 node	20	13 (65.0)	5 (25.0)	0 (0)	2(10.0)	
2 nodes	5	3 (60.0)	1 (20.0)	0 (0)	1 (20.0)	
≥ 3 nodes	4	1 (25.0)	2 (50.0)	1 (25.0)	0 (0)	

We divided patients into two groups using a cut-off of Ki-67 of 14% according to the St Gallen consensus [37]. Patients with Ki-67 ≥ 14% were categorized as the high Ki-67 group, and those with Ki-67 < 14% as the low Ki-67 group. There was no significant association between Ki-67 expression and SLN metastasis.

Non-SLN metastasis and clinicopathological factors

Non-SLN metastasis was in detected in 12 out of the 29 positive SLN patients (41.4%). Among non-SLN metastases, only one positive node was observed in eight patients (66.7%), two positive nodes were observed in one patient (8.3%), and more than three positive nodes were observed in three patients (25%). A total of 16 patients (64.0%) with SLN metastasis showed two or less positive nodes with no further axillary node metastasis but nine patients (36.0%) had non-SLN metastasis. More than three non-SLN metastases were observed in three patients (12%) with SLN metastasis with two or less positive nodes (Table 3).

Clinicopathological factors were examined in the patients with non-SLN metastasis, but there significant association was observed between non-SLN metastasis and clinicopathological factors (Table 4).

Discussion

SLNB for clinically node-negative breast cancer has become a standard procedure worldwide and it is important to determine pathologically whether the node is negative before surgery. In this study, we observed that age, tumor size and LVI are significantly associated with SLN metastasis. Parameters such as a patient age of less than 50 years, large tumor size and prominent LVI were shown to indicate a higher likelihood of the patient being SLN positive. These findings are in accordance with previous reports [11-17], which have also indicated HR and histological grade are good predictors for positive SLN [11, 14, 16, 17]. We could not find any association between HR status/histological grade and SLN metastasis. The discrepancy between previous reports and our results may result from the different relative numbers of patients in each category with 89.2% HR positive and 78.4% grade I in this study.

In contrast to previous reports, this study did not find any association between the molecular subtype and SLN metastasis [3, 10, 18-26]. One possible explanation for the discrepancy between previous reports and our results is the distribution among subtypes, which could affect the results. The HER2 type was very infrequent (3.4%), which may contribute to the absence of SLN metastasis in the HER2 subtype in this study.

The ACOSOG Z0011 study [6] showed that SLNB alone without ALND results in extremely low locoregional recurrence and excellent overall survival comparable to completed ALND in patients with SLN metastasis at two or fewer nodes. We showed that there is greater than 30% risk of non-SLN metastasis, and more than 10% of patients risk having three or more metastases nodes, even if there is SLN metastasis in two or fewer nodes. Our results are comparable to the ALND group in the ACOSOG Z0011 study with similar overall survival and disease-free survival in both groups. Systemic therapy and radiation therapy may have contributed to these results with more than 95% of patients in each group received ajduvant systemic therapy, and more than 88% of patients in each group receiving whole-breast radiation therapy. The possibility exists that more advanced disease in the ALND group was cured by the aggressive ALND procedure. The baseline characteristics of the ACOSOG Z0011 study showed that the number of patients with LN metastasis at one or fewer nodes in the SLND alone group was higher than the ALND group. Systemic therapies includ-

Table 4. Association Between Non-SLN Metastasis and Clinicopathological Features (n = 29)

	Total	SLN		P value
		Negative (%)	Positive (%)	
Age				0.3625
≤ 50	15	10 (66.7)	5 (33.3)	
> 50	14	7 (50.0)	7 (50.0)	
Tumor size				0.8888
T1	16	10 (62.5)	6 (37.5)	
T2	11	6 (54.5)	5 (45.5)	
T3	2	1 (50.0)	1 (50.0)	
Histological grade				0.0618
I	19	14 (73.7)	5 (26.3)	
II	5	1 (20.0)	4 (80.0)	
III	5	2 (40.0)	3 (60.0)	
LVI				0.0638
Negative	22	15 (68.2)	7 (31.8)	
Positive	7	2 (28.6)	5 (71.4)	
ER and/or PR				0.7975
Negative	2	1 (50.0)	1 (50.0)	
Positive	27	16 (59.3)	11(40.7)	
HER2				0.3527
Negative	24	15 (62.5)	9 (37.5)	
Positive	5	2 (40.0)	3 (60.0)	
Molecular subtypes				0.8888
Luminal A	16	10 (62.5)	6 (37.5)	
Luminal B	11	6 (54.5)	5 (45.5)	
HER2	2	1 (50.0)	1 (50.0)	
Triple negative				0.7276
Ki-67				
Ki-67 < 14%	18	11 (61.1)	7 (38.9)	
Ki-67 ≥ 14%	11	6 (54.5)	5 (45.5)	

SLN: sentinel lymph node; LVI: lymphovascular involvement; ER: estrogen receptor; PR: progesterone receptor.

ing hormone therapy, cytotoxic chemotherapy and/or molecular targeting drugs remain highly important in breast cancer treatment. In addition, surgeons who have a critical role in breast cancer treatment should be trained to master the less invasive skill of ALND.

Conclusion

SLN metastasis was associated with younger age, large tumor size and prominent LVI. Non-SLN metastasis was apparent in more than 30% of cases even if SLN metastasis occurred in two or less nodes. Non-SLN metastasis was hard to predict by clinicopathologic factors.

Financial Disclosure

We declare that we have no conflict of interest.

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