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Original Article

High risk for non-sentinel node metastasis in breast cancer patients with sentinel node metastases

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Abstract: Background: To identify the risk factor of non-sentinel lymph node metastasis in breast cancer patients with sentinel lymph node metastasis in order to better guide the decision regarding axillary lymph node dissection (ALND) in breast cancer patients with 1-2 positive sentinel node metastases. Methods: A total of 215 patients with 1-2 positive sentinel lymph nodes (SLNs) who underwent ALND at Department of Breast at the Women's Hospital were reviewed. Independent clinicopathological factors predicting the non-SLN metastasis were analyzed using logistic regression analysis. A risk score was established to predict the non-SLN metastasis. Results: Multivariate logistic regression analysis revealed that increasing tumor size, presence of lymphovascular invasion, HER2 positivity were independent predictors of non-SLN metastasis. Besides, absent of negative SLNs was also an independent risk factor of non-SLN metastasis. Eighty-seven (40.5%) patients had non-SLN metastasis when 1-2 SLNs were positive. Thirty-three (15.3%) patients were classified as high risk of non-NSN metastasis according to the risk score, among which, there were 30 patients (90.9%) with non-SLN metastasis. Conclusion: ALND is beneficial in patients who met eligible for Z0011 criteria but at high risk of non-SLN involvement.

Keywords: Breast cancer, non-sentinel lymph node, axillary lymph node dissection, nomogram

Introduction

Axillary management in breast cancer has changed dramatically from routine axillary lymph node dissection (ALND) to sentinel lymph node (SLN) biopsy has been gradually replaced axillary lymph node dissection (ALND) as standard procedure for axillary management in breast cancer. In patients with negative SLNs, ALND can be safely avoided [1, 2]. While the indication for avoiding ALND has extended from patients with negative SLNs to part of patients with positive SLNs. It has been reported ALND is not beneficial in a subset of patients with SLNs. These patients with completion ALND appeared to have similar recurrence rate or disease-free survival with those without receiving ALND [3]. Moreover, the postoperative arm morbidity of ALND cannot be ignored [4].

The results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial have changed the standard surgical strategy in breast cancer [1, 2, 5]. Patients with 1-2 positive SLNs treating with breast conserving surgery and radiation may avoid axillary lymph node dissection (ALND). However, it was not reported whether the findings from the Z0011 trial hold true for patients undergoing mastectomy without radiation. For these patients, whether to perform ALND is under debate. Previous studies indicated that patients with macrometastatic SLNs have high risk of non-SLN positivity [6-8]. Some studies suggested that it may be unnecessary to perform ALND on patients with micrometastases in SLNs and the presence of micrometastases in SLNs may not be associated with prognosis [9, 10]. In addition, immunohistochemistry is currently not a part of the routine assessment of the SLN intraoperative in most of hospitals. Our current study aimed to investigate the high risk factors of non-SLN metastasis in breast cancer patients with 1-2 positive SLNs who undergo mastectomy, and developed a risk score to

Table 1. Comparison of clinicopathological characteristics of breast cancer patients with or without non-SLN metastasis

Factors	Non-SLN		*P*
	Negative (%)	Positive (%)	
Age (years)			0.153
≤50	100 (78.1)	60 (69.0%)	
>50	28 (21.9)	27 (31.0%)	
Tumor size (cm)			<0.001
>0.5, but ≤1	17 (13.2)	4 (4.6)	
>1, but ≤2	61 (47.7)	22 (25.3)	
>2, but ≤3	33 (25.8)	35 (40.2)	
>3, but ≤4	11 (8.6)	17 (19.5)	
>4, but ≤5	6 (4.7)	9 (10.4)	
Positive SLN			0.264
1	110 (85.9)	69 (79.3)	
2	18 (14.1)	18 (20.7)	
Negative SLN			0.001
0	25 (19.5)	36 (41.4)	
≥1	103 (80.5)	51 (58.6)	
Multifocality			1.000
Multifocal	3 (2.3)	2 (2.3)	
Unifocal	125 (97.7)	85 (97.7)	
lymphovascular invasion			0.022
Yes	4 (3.1)	10 (11.5)	
No	124 (96.9)	77 (88.5)	
ER status			0.384
Yes	87 (68.0)	54 (62.1)	
No	41 (32.0)	33 (37.9)	
PR status			0.165
Positive	69 (53.9)	38 (43.7)	
Negative	59 (46.1)	49 (56.3)	
HER2 status			<0.001
Positive	23 (18.0)	40 (46.0)	
Negative	105 (82.0)	47 (54.0)	
Ki67 status			0.058
Positive	78 (60.9)	64 (73.6)	
Negative	50 (39.1)	23 (26.4)	
Total	128	87	

Note: SLNs with macrometastasis were considered to be positive and SLNs with micrometastasis or ITC or negative with IHC were considered to be "negative".

identify high risks patients for whom ALND may be recommended.

Patients and methods

Patient population

Patients who had 1-2 SLNs metastasis and willing to receive ALND were enrolled in the study during period of January 2013 to October 2015, in Department of Breast, Women's Hospital, School of Medicine, Zhejiang University, China. All the patients enrolled had clinically negative axillary lymph nodes and no previous systemic treatment. Clinicopathological characteristics, including age, tumor size, presence of multiple lesions, presence of lymphovascular invasion, number of positive SLNs, number of negative SLNs, hormone receptor status, HER2 status and Ki67 were retrospectively retrieved and analyzed.

Surgery procedure

Lymphatic mapping for SLN biopsy was performed using blue dye (company). Blue dye was injected into the subareolar and peritumoral region of each subject 5 minutes before SLN biopsy. During the operation, we generally found the blue-stained lymphatics on the lateral border of the pectoralis major muscle through the blue-stained lymph tube. An SLN was defined as any blue-stained node, any node with a blue-stained lymphatic channel leading directly to it.

Pathological evaluation

Intraoperative frozen section analyses were routinely performed on every harvested SLN and a level I and II ALND was performed by consent of the patient if the SLN was positive. Immunohistochemical staining was routinely used in the diagnosis of SLN metastasis postoperatively. The SLN metastasis was classified into macrometastasis, micrometastasis and (isolated tumor cells) ITC according to the American Joint Committee on Cancer (AJCC) 7th Edition [11]. SLNs with macrometastasis were considered to be positive, SLNs with micrometastasis or ITC or negative with IHC were considered to be "negative". In addition, every node was postoperatively examined using hematoxylin and eosin (H&E) staining of serial sections.

All the tumors were invasive carcinoma of no special type (NST) according to the WHO classification of breast tumor 4th Edition [12]. Tumor with 10% or greater positivity was considered as positive for estrogen receptor and

Table 2. Multivariate logistic regression to test the association of each variable with the likelihood of non-SLN metastasis

Variables	Odds ratio	95% CI	*p* value
Tumor size	0.6776	1.429-2.713	<0.001
SLN negative	-0.9180	0.197-0.808	0.011
LVI	1.9060	1.654-27.356	0.008
HER-2	1.4508	2.010-9.059	<0.001

progesterone receptor. For HER2, diffusely stained tumors (triple-positive) or tumors with positive fluorescent in situ hybridization (FISH) test (double-positive tumors) were taken as positive. Ki67 index lower 20% was considered as negative.

Ethics statement

The use of human clinical materials and protocols were approved by the Ethical Committee of Women's Hospital, School of Medicine, Zhejiang University. All patients gave written informed consent.

Statistics analysis

The association between clinicopathological features and lymph node metastasis was evaluated using univariate and multivariate analysis. Categorical variables in univariate analysis were compared using the two-tailed Fisher exact test or the chi-square test. Multivariate analysis was performed using logistic regression analysis. All the data were analyzed using SAS 9.3 statistical software (SAS Institute Inc.). A *P*-value <0.05 was considered statistically significant.

Results

Patient demographics

A total of 215 patients (mean age 47.5 ± 10.2 years) who had 1-2 positive sentinel lymph nodes (SLNs) undergoing ALND were included for analysis. Distribution of variables between patients with and without non-SLN metastases are shown in **Table 1**. The mean pathological tumor size was 2.46 ± 1.06 cm (range 0.6-5.0). In the study population, the mean number of SLN identified was 2.58 (range 1-5). Non-SLN metastasis was found in 87 of 215 patients (40.5%), with an average number of 1.46 (range 1-3) non-SLNs involved.

Risk factors for non-SLN metastasis in breast cancer with one or two positive SLNs

Univariate analysis of the patients with additional metastases on non-SLN and those with no additional metastases on non-SLN are shown in **Table 2**. Significant differences were found between the two groups in tumor size, presence of lymphovascular invasion, presence of negative SLN and HER2 status. In the multivariate analysis, increasing tumor size, negative SLN<1, present of lymphovascular invasion, HER-2 positivity were independent risk factors of non-SLNs metastasis.

Using the formula of the logistic regression model, a patient's probability of non-SLNs metastasis (the risk score) based on the clinicopathological profile was established: P=1/[1+exp(2.6194-0.6776* tumor size +0.918* negative SLN -1.906* lymphovascular invasion status -1.4508* HER2 status)]. In the model, 33 of 215 patients (15.3%) were classified as high risk of non-NSN metastasis, and 30 of these 33 patients (90.9%) had non-SLN metastasis actually.

Discussion

Several predictive tools, including the Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram, the Stanford nomogram have been created over the past years to predict the risk of non-SLN metastasis [13, 14]. However, neither of them is perfect and these studies were not performed in patients with 1-2 positive SLNs. Breast surgeons may worry about the risk of remnant non-SLN metastasis if they do not perform ALND. Thus, predictions of non-SLN metastasis for patients with 1-2 positive SLNs are still necessary nowadays. In a multivariate analysis, we identified increasing tumor size, negative SLN<1, present of lymphovascular invasion, HER2 positivity as independent risk factors for non-SLNs metastasis. By these risk factors, patients with 1-2 positive SLNs could be classified into risk group according to the risk of non-SLN metastasis.

Since the aim of this study is to find patients with high risk of non-SLN for whom ALND was needed, only macrometastatic SLNs were considered as "positive SLN". Previous studies have found that more negative SLNs identified will improve the accuracy of SLN biopsy [7, 15].

However, the procedure looking for more SLN may lead to some unnecessary injury. Our study revealed that one or more negative SLN identified may improve the accuracy of SLN biopsy. Therefore, at least one negative is necessary when SLN biopsy is carried out.

A good predictive nomogram depends on not only its predictive ability but also its clinical utility convenience. Stanford nomogram with 3 variables was reported to be comparable to the MSKCC nomogram with 9 variables [15, 16]. In our study, the risk score model is simple and all the risk factors are routinely available. In the present study, 90.9% of the patients with "high risk" had non-SLN metastasis actually. Since the high rate of non-SLN metastasis actually, ALND is recommended for these patients at a high risk of non-SLN involvement, even if they met the Z0011 criteria. For other patients in whom P<0.5, we propose to avoid ALND for patients who meet the Z0011 criteria.

Increasing tumor size, negative SLN<1, present of lymphovascular invasion, HER2 positivity were independent risk factors of non-NSLN metastasis. Tumor size and HER-2 status can be obtained according to core needle biopsy before surgery. Negative SLN can be achieved in most patients. Although presence of lymphovascular invasion is confirmed after surgery, only few patients have lymphovascular invasion. According to the formula P=1/[1+exp (2.6194-0.6776* tumor size +0.918* negative SLN -1.906* lymphovascular invasion status -1.4508* HER2 status)]. If negative SLN can be found and absent of lymphovascular invasion is absent, P>0.5 when tumor size >3 cm and HER-2 positivity. Hence, ALND should be considered when tumor size >3 cm and HER-2 is positive according to core needle biopsy before surgery.

In addition to the risk factors presented in previous studies, HER2 positivity correlated with the likelihood of non-SLN metastasis in our patient population. Some studies have also identified HER2 status to be significantly predictive of further axillary lymph node involvement [17, 18]. The implication of HER2 on recurrence and survival is well documented, but exactly how HER2 status influences SLN and non-SLN involvement remains to be clarified.

For the foreseeable future, more nomograms will be developed in order to avoid unnecessary ALND. The aim of our scores in this study is to identify a subgroup of patients, especially in those with 1-2 positive SLNs, with a high risk for non-SLN involvement, regardless of whether mastectomy or breast-conserving treatment. Necessary ALND should still be carried out in patients at a high risk of non-SLN metastasis, avoiding inadequate treatment. However, our nomogram has some limitations. Some patients with non-SLN metastasis were still not detected by the nomogram. In consideration of clinical utility convenience, all the predictive factors in this study can be achieved in most hospitals. In order to enhance its strength, more predictive factors should be enrolled, especially in large medical centers.

Conclusion

High risk factors routinely available were identified and a nomogram for non-SLN metastasis were established. ALND is recommended for patients at high risk of non-SLN involvement, even if they met the Z0011 criteria. For other patients, ALND would be avoided if they meet the Z0011 criteria.

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Disclosure of conflict of interest

None.

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