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Role of number of sentinel nodes in predicting non-sentinel node metastasis in breast cancer

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Abstract

Objective: The aim of the present study was to determine how many sentinel lymph nodes (SLNs) are appropriate for predicting non-SLN metastasis in breast cancer.

Methods: The association between clinicopathological features and non-SLN metastasis was retrospectively analyzed in 472 patients who underwent axillary lymph node dissection (ALND) following SLN biopsy. Another 251 patients who underwent only SLN biopsy without ALND were analyzed and followed up for 2 years.

Results: A large tumor size, positive SLN, and HER-2 positivity were independent predictors of non-SLN metastasis. There were significant differences in non-SLN metastasis between patients with one negative SLN and patients with an absence of negative SLNs. There was no significant difference in non-SLN metastasis between patients with one negative SLN and two or more negative SLNs. The recurrence-free survival rate for patients who did not undergo ALND was 99.6% (245/246).

Conclusion: Surgeons should ensure that the number of SLNs obtained is appropriate. The presence of one negative SLN is enough in SLN biopsy. Considering the invasiveness of the surgery, two or more negative SLNs may be unnecessary.

Keywords

Breast cancer, non-sentinel lymph node, axillary lymph node dissection, sentinel lymph node, metastasis, biopsy

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Introduction

Axillary management in breast cancer has evolved from routine axillary lymph node dissection (ALND) to sentinel lymph node (SLN) biopsy. The SLN is the first lymph node to receive lymphatic drainage from a tumor and theoretically the first site of lymphatic metastasis. In the 1990s, SLN biopsy (SLNB) was developed as a surgical technique for the local axillary lymph nodes in patients with breast cancer.[1] This technique was a landmark in the development of breast surgery and has become an important part of the standard treatment of early breast cancer.

Large-scale clinical trials have confirmed that SLNB and ALND show no significant differences in disease-free survival, overall survival, or recurrence-free survival in SLN-negative patients,[2–4] and SLNB can accurately predict axillary lymph node metastasis. Many nomograms have also been developed to predict the risk of non-SLN metastasis to avoid unnecessary ALND. The findings of the Z0011 trial changed the standard surgical paradigm in breast cancer by showing that patients with breast cancer with one to two positive SLNs who are treated with conservative breast surgery may avoid ALND.[5] The number of negative SLNs has been identified as an independent predictor of non-SLN metastasis,[6] and the presence of negative SLNs may reduce the risk of residual disease in non-SLNs. In principle, SLN-negative patients can avoid ALND; however, the procedure by which the SLN itself is obtained may lead to unnecessary injury. Hence, it is important to clarify whether the identification of more SLNs is beneficial. Accordingly, the objective of this study was to determine how many SLNs are needed to predict non-SLN metastasis in patients with breast cancer.

Methods

Patients

Patients with stage cT1-2 N0 breast cancer who underwent SLNB from January 2013 to July 2015 in the Department of Breast, Women's Hospital, School of Medicine, Zhejiang University, China were included in the present study. None of the enrolled patients had undergone previous systemic treatment.

Surgical procedure and pathological evaluation

Lymphatic mapping for SLNB was performed using blue dye. Blue dye was injected into the subareolar and peritumoral regions of each patient 5 minutes before SLNB. During the operation, we generally observed the blue-stained lymphatics on the lateral border of the pectoralis major muscle through the blue-stained lymph tube. We then separated the blue-stained lymph nodes as the SLNs.

Intraoperative frozen section analyses were routinely performed for every harvested SLN. Patients with negative SLNs underwent ALND or no further axillary treatment. ALND was avoided in patients with positive SLNs if they met the Z0011 criteria; otherwise, level I or II ALND was performed.

Informed consent was obtained from all patients, and all procedures performed were in accordance with the ethical standards of the responsible committee on human experimentation in the Women's Hospital, School of Medicine, Zhejiang University. Immunohistochemical staining was routinely performed to obtain a preoperative diagnosis of SLN metastasis. The SLN metastasis was classified as macrometastasis (MAC), micrometastasis, or isolated tumor cells according to the American Joint Committee on Cancer

7th Edition.[7] In addition, every node was postoperatively examined using hematoxylin and eosin staining of serial sections.

Adjuvant therapy

All patients were treated according to the National Comprehensive Cancer Network guidelines. Radiotherapy was performed for patients who underwent conservative breast surgery and patients with positive lymph nodes. Chemotherapy regimens were based on anthracyclines and taxanes, and hormone therapy was based on tamoxifen and aromatase inhibitors. From 2005, adjuvant trastuzumab therapy was used for HER-2-positive patients.

Evaluation

All tumors were invasive carcinoma of no special type according to the World Health Organization Classification of Breast Tumors, 4th Edition.[8]

In the evaluation of estrogen or progesterone receptor positivity, a 10% positive rate for each parameter was considered positive. For HER-2, diffusely stained tumors (triple-positive) or tumors with positive fluorescent in situ hybridization results (double-positive tumors) were considered positive. A Ki67 index of $<14\%$ was considered negative.

Follow-up

Patients who did not undergo ALND were followed up. All patients were clinically examined every 3 months in the first year postoperatively, then every 6 months thereafter. Examinations involved assessment of the breasts or chest wall, axillae, and supraclavicular fossae. An annual mammogram was performed. Dedicated breast ultrasound was also performed if necessary. Other hematological and imaging examination were performed according to the clinical situation.

Statistical analysis

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

Results

Patients who underwent ALND

In total, 723 patients with stage cT1-2 N0 breast cancer underwent SLNB. The characteristics of the patients who underwent ALND ($n = 472$) are provided in Table 1. Their mean age was 48.5 years (range, 27–80 years). The mean pathological tumor size was 2.38 cm (range, 0.6–5.0 cm). In total, 56.4% of the SLNB findings were negative. In all patients with positive SLNs, 73.8% had only one positive SLN, 20.5% had two positive SLNs, and 5.6% had three or more positive SLNs. The false-negative rate (FNR) was 5.50% (12/218). A large tumor size ($P = 0.0012$), SLN positivity ($P < 0.0001$), and HER-2 positivity ($P = 0.0229$) were independent predictors of non-SLN metastasis (Table 2).

Association between number of positive/negative SLNs and non-SLN metastasis

The association between the number of positive/negative SLNs and non-SLN metastasis was analyzed (Table 3).

Table 1. Comparison of characteristics of patients with breast cancer with negative versus positive non-SLNs

Characteristic	Non-SLN negativity	Non-SLN positivity	P
Age (years)			0.2850
≤50	278	51	
>50	115	28	
Tumor size (cm)			0.0005
>0.5, but ≤1	46	3	
>1, but ≤2	164	19	
>2, but ≤3	120	33	
>3, but ≤4	46	18	
>4, but ≤5	17	6	
Positive SLN			<0.0001
0	254	12	
≥1	139	67	
Negative SLN			<0.0001
0	19	20	
≥1	374	59	
Total SLN			0.3642
1	107	21	
2	133	21	
≥3	153	37	
Multifocality			0.4640
Multifocal	10	3	
Unifocal	383	76	
Lymphovascular invasion			0.2479
Present	17	6	
Absent	376	73	
Estrogen receptor status			1.0000
Positive	251	50	
Negative	142	29	
Progesterone receptor status			0.7114
Positive	191	36	
Negative	202	43	
HER-2 status			0.0012
Positive	73	30	
Negative	284	43	
Unknown	36	6	
Ki67 status			0.1741
Positive	235	56	
Negative	155	23	
Unknown	3	0	
Total	393	79	

Data are presented as numbers of patients. SLN, sentinel lymph node

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

Variables	Odds ratio	95% CI	P
Tumor size	0.4928	1.215–2.206	0.0012
Positive SLN	1.9903	3.230–16.577	<0.0001
Negative SLN	−1.4113	0.081–0.737	0.0124
HER-2 positive	0.7808	1.114–4.277	0.0229

CI, confidence interval; SLN, sentinel lymph node

Table 3. Association between number of positive/negative SLNs and non-SLN metastasis

	Non-SLN negativity	Non-SLN positivity	P
Positive SLNs			
0	254	12	<0.0001[a]
1	109	46	0.2536[b]
2	24	16	0.7442[c]
≥3	6	5	
Negative SLNs			
0	19	20	<0.0001[a]
1	144	25	0.8665[b]
2	109	17	0.8548[c]
≥3	121	17	

[a]Compared with patients with ≥1 positive or negative SLN; [b]Compared with patients with ≥2 positive or negative SLNs; [c]Compared with patients with ≥3 positive or negative SLNs.

A significant difference in non-SLN metastasis was found between the absence of positive/negative SLNs and the presence of one or more positive/negative SLNs (P<0.0001). There was no significant difference in SLN metastasis between the presence of one positive/negative SLN and two or more positive/negative SLNs.

Patients who did not undergo ALND

The descriptive characteristics of the patients who did not undergo ALND

($n = 251$) are provided in Table 4. Five of 251 patients (2.0%) were lost to follow-up. The mean age of the patients who did not undergo ALND was 51.48 years (range, 23–82 years). The mean pathological tumor size was 1.76 cm (range, 0.6–5.0 cm). Of the four patients who underwent mastectomy, the SLN of one patient was positive on frozen section, but she refused ALND because of her old age. The SLNs of the other three patients were negative on frozen section; however, although the final paraffin section was positive, these patients refused ALND after mastectomy. Two patients with micrometastases and two with isolated tumor cells underwent mastectomy without ALND. Ten patients with one positive SLN underwent breast-preserving surgery without ALND. The median patient follow-up time was 34.0 months, and the mean was 32.9 months (range, 12–74 months). No patients developed recurrence in the axilla. One patient developed recurrence in the same breast 2 years after breast-preserving surgery. Modified radical mastectomy was performed in this patient, and no lymph node metastasis was detected. In this patient, the tumor size was 2.0 cm, estrogen and progesterone receptors were negative, and HER-2/neu receptor was positive. She underwent chemotherapy and biological therapy. All other patients survived without recurrence. The recurrence-free survival rate was 99.6% (245/246).

Table 4. Characteristics of patients with breast cancer who did not undergo axillary lymph node dissection

Characteristic	Patients (n)
Age (years)	
≤50	133
>50	118
Tumor size (cm)	
>0.5, but ≤1	76
>1, but ≤2	111
>2, but ≤3	49
>3, but ≤4	10
>4, but ≤5	5
Positive SLNs	
0	237
1	14
2	0
≥3	0
Negative SLNs	
0	0
1	159
2	92
≥3	0
Surgery	
Breast-preserving	110
Mastectomy	141
Multifocality	
Multifocal	7
Unifocal	244
Lymphovascular invasion	
Present	5
Absent	246
Estrogen receptor status	
Positive	173
Negative	78
Progestrone receptor status	
Positive	129
Negative	122
HER-2 status	
Positive	57
Negative	194
Ki67 status	
Positive	203
Negative	48
Total	251

SLN, sentinel lymph node

Discussion

The SLN is considered the first node that receives direct lymphatic drainage from the tumor. However, it is commonly believed that even for the most experienced surgeons, SLNB is associated with a high FNR. Pecha et al.[9] reported an FNR of 5% in patients with an original tumor of <2 cm in size, 9% for tumors of 2 to 4 cm, and 13.8% for tumors of >4 cm.

Gimbergues et al.[10] reported an FNR of 5.7% in patients with T1-T2 cancer but 28.5% in patients with T3 cancer ($P = 0.045$), confirming the close correlation between the FNR of SLNB and tumor volume. Thus, it is widely known that SLNB is mostly suitable for patients with T1-T2 cancer. In large tumors with an increased rate of lymphatic metastasis, the metastatic cancer cells often clog the lymphatic channels, changing the original lymphatic circulation and thus hindering the normal transfer of the imaging agent or radionuclide in the lymphatic vessels. One systematic review of 24 studies showed that the combined use of a radioisotope and blue dye had a higher identification rate of SLNs than a radioisotope alone.[11] Dual tracers did not significantly reduce the FNR compared with a radioisotope alone. Moreover, an overview of 69 studies of SLNB validated by concurrent ALND confirmed an SLN identification rate of 96%, with an average FNR of 7%.[12] In the present study, the FNR was 5.48% in patients who underwent ALND. Other researchers have reported that peripheral lymph node sampling[13] or atrial ALND[14] may further reduce the FNR of SLNB. However, more extensive surgery may lead to more unnecessary injury.

In general, SLN metastases are identified in about 30% of patients with clinically node-negative breast cancer, and half of those with positive SLNs have only SLN metastases.[15] Conversely, 40% of patients with MAC in the SLN have a higher probability of non-SLN metastases. Wada and Imoto[16] calculated the probability of non-SLN metastases using predictive factors for patients with SLN-positive breast cancer who underwent SLNB followed by ALND. They demonstrated that the tumor size, size of the largest SLN metastasis, proportion of positive SLNs among all SLNs detected, and lymphatic invasion of the tumor were independent predictive factors for non-SLN metastases. Among the patients with cT1-2 N0 breast cancer who underwent ALND, 51.3% had negative lymph node metastasis, 40.5% had one to two positive lymph nodes, and only 5.7% had three or more lymph node metastases. Hence, a higher number of SLNs obtained is not necessarily beneficial.. Three or fewer SLNs is enough for most patients. The results of the present study revealed that the presence of one negative SLN is necessary for SLNB. Moreover, there was no significant difference between the presence of one negative SLN and two or more negative SLNs. Hence, in consideration of surgical injury, obtaining two or more negative SLNs may be unnecessary. Therefore, when one or two positive SLNs are detected, one negative SLN is needed to avoid ALND. When three or more positive SLNs are detected, ALND should be carried out. For patients with negative SLNs, one to three SLNs is enough.

A large tumor size and HER-2 positivity were also identified as independent predictors of non-SLN metastasis. Therefore, when a patient has a large tumor size or HER-2 positivity, the surgeon should pay more attention to the possibility of non-SLN metastasis, and acquisition of one to two negative SLNs should be assured. Intraoperative detection of metastatic carcinoma in SLNs leads to immediate ALND, avoiding the need for a delayed second surgical procedure. Frozen section is often the preferred method for intraoperative evaluation. One meta-analysis of 47 studies involving frozen section revealed a pooled sensitivity of 73%, and the sensitivity for MAC was higher than that for micrometastases (94% vs. 40%, respectively).[17] Wong et al.[18] retrospectively reviewed 2202 SLNBs from 2174 patients with breast carcinoma at Singapore General Hospital during a 7-year period. The authors confirmed the relationship between the size of the SLN metastasis and the risk of a false-

negative frozen section result. The also identified an overall FNR of 13.5%, and the FNR for detection of MAC was much lower at 3.1%. The smaller the SLN metastases, the higher the odds of a false-negative diagnosis. Rapid molecular techniques for intraoperative detection of metastatic carcinoma in SLNs are also available, but they have somewhat questionable sensitivity. However, with the wide application of the Z0011 trial, intraoperative diagnosis of SLNs and prediction of the non-SLN status have become less important.

In conclusion, research of false-negative SLNBs in patients with breast cancer has facilitated more evidence-based medicine and enabled the development of new methods with which to reduce the FNR of SLNB. With the modified indications for SLNB, the demands on technology are increasing to assure a high success rate and low FNR, which will benefit patients. Refinements of SLNBs require not only the efforts of surgeons but also the cooperation of clinicians in radiology, nuclear medicine, and pathology, making SLNB the most reliable measure in axilla-conserving treatment. Developments are moving in the direction of minimally invasive surgery. SLN-guided surgery has been widely accepted by breast surgeons. In accordance with minimal invasiveness, SLNB should avoid unnecessary injury. Assurance of the appropriate number of SLNs is important.

Abbreviations

SLN = sentinel lymph node
ALND = axillary lymph node dissection
SLNB = sentinel lymph node biopsy
FNR = false-negative rate
MAC = macrometastases

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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