Imaging Predictors for Nonsentinel Lymph Node Metastases in Breast Cancer Patients

Yizi Cong^a Suxia Wang^b Haidong Zou^a Shiguang Zhu^a Xingmiao Wang^a
Jianqiao Cao^a Ji Wang^a Yanqing Liu^a Guangdong Qiao^a

^aDepartment of Breast Surgery, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China;

^bDepartment of Pathology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China

Keywords

Breast neoplasms · Sentinel lymph node biopsy ·
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Abstract

Background: The relationship between imaging features and nonsentinel lymph node (NSLN) metastasis is not clear.

Objectives: To determine whether imaging features could predict NSLN metastasis in sentinel lymph node (SLN)-positive breast cancer patients and to provide new clues for avoiding unnecessary axillary lymph node dissection.

Method: 171 patients with clinically negative axillary lymph nodes and a pathologically positive SLN were recruited between January 2007 and January 2014. According to the Breast Imaging Reporting and Data System (BI-RADS), the effects of clinicopathological factors, especially imaging features, on NSLN metastases were assessed by univariate and multivariate statistical analyses. **Results:** The average number of dissected SLNs was 2.11 (range, 1–6); 56 of the 171 (32.75%) patients exhibited NSLN metastases. In univariate analysis, tumor size, number of positive SLNs, ratio of positive SLNs, mammographic mass margins, ultrasonographic mass margins, and ultrasonographic vascularity were significantly correlated with NSLN involvement. Furthermore, through multivariate analysis, tumor size, number of posi-

tive SLNs, mammographic mass margins, and ultrasonographic vascularity were still independent predictors of NSLN involvement. Additionally, in SLN-positive patients, number of positive SLNs and ultrasonographic vascularity could also predict the tumor burden in NSLN. **Conclusions:** In addition to tumor size and the number of positive SLNs, mammographic mass margins and ultrasonographic vascularity were also independent predictors of NSLN metastases in SLN-positive patients of breast cancer. The number of positive SLNs and ultrasonographic vascularity could also predict the tumor burden in NSLN.

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Introduction

Sentinel lymph node biopsy (SLNB) is the standard treatment for breast cancer patients with clinically negative axillary lymph nodes. Although axillary lymph node dissection (ALND) has higher morbidities than SLNB, it is still a standard procedure for patients with a positive SLN, except for patients that fit the ACOSOG Z0011 criteria [1]. However, 40–60% of patients have been found to lack non-

Yizi Cong and Suxia Wang contributed equally to this study.

sentinel lymph node (NSLN) involvement after ALND, indicating that these patients received unnecessary ALND [2]. Thus, it is quite important to identify patients with SLN involvement only but without NSLN metastases.

Over the past few years, multiple studies have been conducted to identify the clinicopathological factors that could predict NSLN metastases, including the method of detection (hematoxylin and eosin, HE), SLN metastases >2 mm in size, extracapsular extension in the SLN, >1 positive SLN, ratio of positive sentinel nodes >50%, tumor size >2 cm, and lymphovascular invasion in the primary tumor [2, 3]. Furthermore, some mathematical models have been developed to predict the NSLN status [4–6]. However, the predicted probability of these models was not very high. Therefore, new factors are needed to help improve the predicted probability.

Mammography and ultrasonography images could reflect alterations in breast anatomy and pathology. Previous studies showed that mammographic tumor features were associated with axillary lymph node metastases in breast cancer patients [7–10], and studies also revealed mammographic spiculation as a positive prognostic marker due to the correlation with low-grade tumors and improved survival [11–13]. Besides, vessels in tumors which could be detected by color Doppler ultrasound were also correlated with lymph node metastases. Based on the above theory, we supposed that mammographic and ultrasonographic tumor features could also predict NSLN metastases.

In this study, we investigated the imaging features that could predict NSLN metastases in breast cancer patients with clinically negative axillary lymph nodes. Through this study, we expected to provide more information for the prediction of NSLN metastases.

Materials and Methods

Patient History

This was a retrospective review study including 537 breast cancer patients with clinically negative axillary lymph nodes who received SLNB from January 2007 through January 2014. Patients treated with neoadjuvant chemotherapy were excluded. No enlarged lymph nodes were palpable, and absence of any suspicious findings on ultrasound was considered axillary negative [14]. Of these patients with clinically negative axillary lymph nodes, 171 patients with a pathologically positive SLN received ALND. The medical records of these 171 patients were retrieved from our registry, and their clinicopathological characteristics were analyzed. All images for this study were reviewed by 2 breast radiologists in our hospital. The mammographic and ultrasonographic features of the tumors in the current study were evaluated according to BI-RADS criteria [15].

Sentinel Lymph Node Biopsy

SLN mapping was performed using lymphoscintigraphy with methylene blue dye. On the day of operation, technetium-99 sulfur

colloid (Beijing Shihong Pharmaceutical Development Center, Beijing, China) was injected intradermally above the tumor, peritumorally, at the areola of the breast, or at the surgical site of the previous biopsy. Scans of the involved breast and axilla were acquired 2 h after tracer injection. Methylene blue dye (Jumpcan, Taixing, China) was injected 15 min before surgery. During surgery, the SLN was localized by using a γ -probe (Neoprobe Corporation, Dublin, OH, USA). The SLN was defined as a blue lymph node and/or a lymph node with an ex vivo radioactive count $\geq 10\%$ of the ex vivo radioactive count of the hottest lymph node. In addition, any clinically suspicious, palpable lymph nodes were also removed.

Pathological Examinations

All SLNs were subjected to standard frozen section evaluation with HE-stained section. The first SLN defined as the bluest or hottest lymph node was bisected longitudinally and frozen; other SLNs were frozen intactly. Frozen sections were taken with a microtome setting of 4 μ m. The remaining nodal tissue was fixed in 10% formalin and embedded in paraffin. After this fixation, serial sections of the SLN were obtained for definitive analysis. The HER2 overexpression status was determined according to the American Society of Clinical Oncology guidelines [16]. According to different combinations of ER, PR, HER2 status, and Ki67, patients were categorized into 4 subgroups as follows: luminal A, luminal B, HER2 overexpression, and triple negative [17].

Statistical Analyses

Statistical analyses were performed using SPSS 19.0 (IBM Corporation, New York, NY, USA). A χ^2 test, Fisher's exact test, and analysis of variance were used to compare patients and tumor characteristics. Multivariable analyses were performed on variables with $p < 0.050$ from the univariable analyses by logistic regression. Independent sample t tests were used to compare the factors which influenced the number of NSLN metastases. A p value of 0.050 or smaller was considered statistically significant.

Results

Baseline Characteristics of the Patients

A total of 171 patients with invasive breast cancer had a positive SLN, and all received ALND. The average number of total metastatic lymph nodes was 1.95 (range, 1–11). The median age of these patients was 49 years (range, 24–75 years). The average number of SLNs dissected was 2.11 (range, 1–6). Of these 171 patients, 56 patients (32.75%) had at least 1 positive NSLN. In patients with 1, 2, or more SLN metastases, the average numbers of NSLN metastases were 0.59 ± 1.258 and 1.18 ± 1.749 ($p = 0.027$). The proportion of patients who had the luminal A subtype was 42.69%, and the proportion of patients with luminal B, HER2 overexpression, and triple-negative subtypes was 37.43, 6.43, and 6.43%, respectively. The subtypes of another 7.02% patients were unclear because of HER2++ on immunohistochemistry without fluorescence in situ hybridization test. Baseline characteristics of these 171 breast cancer patients are shown in Table 1.

Of these 171 patients, 8 patients received tumor resection biopsy in other hospitals, so imaging data were not available. Tables 2 and 3 list the distribution of mammographic and ultrasonographic appearances among 163 patients with available information, and they also show the correlations between these appearances and lymph node status.

Factors Predictive of NSLN Involvement

In the univariate analysis of NSLN metastases (Tables 1–3), larger tumors were more common in the NSLN-positive group than the NSLN-negative group ($p = 0.022$). The number of positive SLNs in the NSLN-positive group was higher than in the NSLN-negative group ($p = 0.000$). However, age at diagnosis ($p = 0.639$), histological grade ($p = 0.134$), SLN number examined ($p = 0.935$), and molecular subtypes ($p = 0.425$) did not show significant differences between these 2 groups. Patients with the luminal A subtype seemed to have a higher risk of NSLN metastases than other subtypes, but there was no statistically significant difference.

On mammography, circumscribed, microlobulated, obscure, and indistinct features were grouped together to provide adequate numbers for comparison with spiculated numbers. We found that masses with spiculated margins were more commonly observed in the NSLN-positive group compared with the NSLN-negative group ($p = 0.030$); breast density, mass shape, calcifications, and associated features did not reveal statistical differences between these 2 groups (Table 2).

Ultrasonographically, proportions of microlobulated and circumscribed margins were merged to compare them with proportions of indistinct, angular, or spiculated margins. Similarly, masses with indistinct, angular, or spiculated margins were more commonly found in the NSLN-positive group ($p = 0.029$). Besides this, Doppler color imaging revealed that masses with internal, rim, or internal plus rim vascularity were more commonly found in the NSLN-positive group, and absence of vascularity occurred more often in the NSLN-negative group ($p = 0.040$) (Table 3).

In multivariate analysis, tumor size ($p = 0.027$), number of positive SLNs ($p = 0.003$), mammographic mass margins ($p = 0.038$), and ultrasonographic vascularity ($p = 0.036$) were all significant predictive factors of NSLN metastasis, while the ratio of positive SLN and ultrasonographic mass margins showed no statistical differences (Table 4).

At last, we analyzed which factors could predict the tumor burden in NSLN. Table 5 indicates that ultrasonographic vascularity ($p = 0.032$) can also predict the tumor burden in NSLN besides the number of positive SLNs ($p = 0.027$). Tumor size ($p = 0.107$) and mammographic mass margins ($p = 0.390$) also tend to predict the NSLN burden, but there was no statistical significance.

Table 1. Characteristics of the breast cancer patients with positive SLNs and univariate analysis of NSLN metastases

Variable	Total (<i>n</i> = 171)	Negative NSLN (<i>n</i> = 115)	Positive NSLN (<i>n</i> = 56)	<i>p</i>
Age				0.639
≤50 years	99	68	31	
>50 years	72	47	25	
Tumor size				0.022
T1	112	81	30	
T2	55	31	25	
NA	4	3	1	
Histological grade				0.134
I	37	29	8	
II	108	71	37	
III	24	13	11	
NA	2	2	0	
SLNs				0.935
1	53	37	16	
2	70	46	24	
3	31	20	11	
≥4	17	12	5	
Positive SLNs				0.000
1	137	101	36	
≥2	34	14	20	
Ratio of positive SLN				0.034
≤50%	87	65	22	
>50%	84	50	34	
Molecular subtype				0.425
Luminal A	73	44	29	
Luminal B	64	45	19	
HER2 overexpression	11	9	2	
Triple negative	11	8	3	
NA	12	9	3	

NA, not available; SLN, sentinel lymph node; HER2, human epidermal growth factor receptor 2; NSLN, non-SLN.

Discussion

SLNB is widely used to assess axillary status in patients with early-stage invasive breast cancer. Generally, ALND is the standard treatment for most patients with a positive SLN. However, the therapeutic efficacy of this procedure is controversial because 40–60% of patients lack NSLN involvement after ALND [2]. In order to avoid unnecessary ALND, many authors have tried to predict in which patients ALND can be safely omitted, and various risk factors for probable NSLN metastases have been identified [3]. In addition, some nomograms have been developed to predict NSLN status [5, 18]. However, the predictive value of these models does not reach the intended high accuracy level. Therefore, new factors and methods are needed to improve the predicted probability.

In this study, we found additional nodal involvement in only 32.75% of patients, which is lower than the reported range of 40–60% [2]. The variation in NSLN in-

Table 2. Mammography findings of breast cancer patients with positive SLNs and univariate analysis of NSLN metastases

Mammography findings	Total (<i>n</i> = 163)	Negative NSLN (<i>n</i> = 108)	Positive NSLN (<i>n</i> = 55)	<i>p</i>
Breast density				
1	27	17	10	0.527
2	37	28	9	
3	64	42	22	
4	35	21	14	
Result				
Normal (BI-RADS 1 or 2)	12	11	1	0.061
Abnormal	151	97	54	
Lesion type				
Mass	89	61	28	0.192
Mass with calcifications	49	30	19	
Calcification only	11	6	5	
Other imaging	2	0	2	
Mass shape				
Oval	15	7	8	0.095
Irregular	123	84	39	
Mass margins				
Circumscribed	7	6	1	0.030 ^a
Microlobulated	8	6	2	
Obscure	6	3	3	
Spiculated	45	24	21	
Indistinct	72	52	20	
Calcifications				
No	104	73	31	0.125 ^b
Typically benign	1	1	0	
Amorphous	5	3	2	
Coarse heterogeneous	6	3	3	
Fine pleomorphic	43	25	18	
Fine linear or branching	4	3	1	
Associated features				
Skin retraction				
Yes	5	3	2	1.000
No	158	105	53	
Nipple retraction				
Yes	12	7	5	0.541
No	151	101	50	
Skin thickening				
Yes	13	7	6	0.366
No	150	101	49	
Mass size, cm		2.056±0.707	2.355±0.773	0.024

^a Circumscribed, microlobulated, obscure, and indistinct numbers were grouped together to provide adequate numbers for comparison with spiculated numbers. ^b No calcification and typically benign numbers were grouped together to provide adequate numbers for comparison with other types of calcifications.

volvement can partly be explained by differences in the size of study populations and rigorous use of preoperative axillary ultrasound. Another reason may be that patients with suspicious lymph nodes on ultrasound who received core needle biopsy were excluded in our study.

Similar to previous research, we also revealed that primary tumor size and the number of positive SLNs were predictors of NSLN metastases. Patients with a tumor size >2 cm had a significantly higher risk of NSLN metastases.

Besides, the NSLN metastasis risk also increased with increasing number of positive SLNs. However, the ratio of positive SLNs and histological grade did not reach significant predictive values. A previous study found significant differences in different subtypes in terms of NSLN metastases [19]. Zhou et al. [20] reported that patients with luminal A and B subtypes had a higher risk of NSLN metastases than those with triple-negative breast cancer. However, in a study by Gülben et al. [21], luminal A subtype of breast

Table 3. Ultrasonographic findings of breast cancer patients with positive SLNs and univariate analysis of NSLN metastases

Ultrasound findings	Total (n = 163)	Negative NSLN (n = 108)	Positive NSLN (n = 55)	p
Mass shape				
Round	1	1	0	0.664 ^a
Oval	4	3	1	
Irregular	158	104	54	
Mass margins				
Circumscribed	10	8	2	0.029 ^b
Indistinct	56	40	16	
Microlobulated	20	17	3	
Angular	60	33	27	
Spiculated	17	10	7	
Orientation				
Parallel	104	68	36	0.754
Not parallel	59	40	19	
Echo pattern				
Hypoechoic	2	2	0	0.301 ^c
Hyperechoic	1	1	0	
Heterogeneous	159	104	55	
Complex cystic and solid	1	1	0	
Posterior feature				
No features	119	80	39	0.489 ^d
Shadowing	42	26	16	
Enhancement	1	1	0	
Combined pattern	1	1	0	
Calcifications				
No	114	78	36	0.373
In mass	49	30	19	
Vascularity				
Absent	36	29	7	0.040 ^e
Internal	91	55	36	
Rim	22	16	6	
Internal + rim	14	8	6	
Mass size, cm		1.934±0.661	2.429±0.883	0

^a Round and oval numbers were grouped together to provide adequate numbers for comparison with irregular numbers. ^b Proportions of microlobulated and circumscribed margins compared with proportions of indistinct, angular, or spiculated margins. ^c Hypoechoic, hyperechoic, and complex cystic and solid were grouped together to provide adequate numbers for comparison with heterogeneous. ^d Category enhancement, no features, and combined pattern were grouped together to allow adequate group size for comparison. ^e Internal, rim, and internal + rim were grouped together to provide adequate numbers for comparison.

cancer had the lowest risk of NSLN metastases, while patients with the luminal/HER2+ subtype had a higher risk of NSLN metastases than those with the luminal A subtype, and the HER2-overexpressing subtype was significantly associated with NSLN metastases. In our previous studies [19–21], molecular subtypes were divided based on ER, (and/or) PR, and HER2 status. Ki67 was also used to distinguish luminal A and B (HER2-negative) subtypes in our study which was different from the above research. Our results revealed patients with the luminal A subtype had a higher risk of NSLN metastases than those with other subtypes, but this difference was not statistically significant, which was in agreement with the study by Zhou et al. [20].

Tumor features on mammography were also related to axillary lymph node metastases in breast cancer patients. Regarding the nodal involvement, previous data demonstrated that pleomorphic calcifications [7, 10], overlying skin thickening, or dimpling on mammogram were more frequently present in the lymph node-positive group [7]. Recently, a study showed that higher probability of malignant calcifications was associated with more lymph node involvement compared with patients with spiculated masses, and a nonstellate mass had a lower risk of lymphatic metastases [8]. However, another study showed that tumors appearing as calcifications were more often ALN negative compared with tumors appearing as a distinct mass;

Table 4. Multivariate analysis of factors affecting NSLN metastases

Variable	OR	95% CI	<i>p</i>
Tumor size			
T1	1	Reference	
T2	2.466	1.109–5.484	0.027
Positive SLNs			
1	1	Reference	
≥2	4.737	1.712–13.107	0.003
Mammographic mass margins			
Circumscribed + microlobulated + obscure + indistinct	1	Reference	
Spiculated	2.37	1.049–5.353	0.038
Ultrasonographic vascularity			
Absent	1	Reference	
Internal, rim, or internal + rim	3.128	1.080–9.059	0.036
Ratio of positive SLN			
≤50%	1	Reference	
>50%	1.005	0.433–2.335	0.99
Ultrasonographic mass margins			
Circumscribed + microlobulated	1	Reference	
Indistinct + angular + spiculated	2.162	0.709–6.595	0.175

OR, odds ratio; CI, confidence interval.

Table 5. Analysis of factors affecting tumor burden in NSLN

Variable	Cases	Positive NSLN ($\bar{x} \pm s$), <i>n</i>	<i>p</i>
Tumor size			
T1	111	0.59±1.351	
T2	56	0.96±1.464	0.107
Positive SLNs			
1	137	0.59±1.258	
≥2	34	1.18±1.749	0.027
Mammographic mass margins			
Circumscribed + microlobulated + obscure + indistinct	93	0.62±1.351	
Spiculated	45	0.82±1.072	0.39
Ultrasonographic vascularity			
Absent	36	0.39±0.934	
Internal, rim, or internal + rim	127	0.83±1.505	0.032

tumors presenting as an ill-defined mass and spiculated appearance tended to be more often ALN positive than tumors which presented as a distinct mass [9]. In our present study, spiculated mammographic margins had a significantly higher risk of NSLN metastases, which was basically consistent with the above 2 studies. Besides, patients with malignant calcification also had a tendency to be more prone to lymph node metastases but without statistical significance. Why was there a relationship between spiculated mammographic margins and NSLN metastases? As previously reported, loss of adhesion factors on carcinoma cells was considered to play a role in the histological appearance of invasive carcinoma as loosely dispersed linear columns of cells and a typical discrete mass [22, 23]. This more diffuse infiltrative pattern may explain some of the typical im-

aging appearances of tumors, such as spiculation and distortion [22]. Thus, based on this theory, we considered that loss of adhesion factors may increase potential lymph node metastases in spiculated mammographic tumors. As to why mammographic spiculation may be a good prognostic marker, another study showed that the spiculation feature was associated with high ER and PR expression [24]. Therefore, we thought that due to the better treatment, especially endocrine therapy, spiculated mammographic tumors could still achieve a good prognosis, although lymphatic metastases are more likely to occur.

Regarding tumor blood supply, it is well established that microvessel formation in tumors is closely correlated with lymph node metastases. Several studies confirmed this theory by Doppler sonography [25–27]. Tumor vascularity

revealed by power Doppler sonography was strongly correlated with the detection of lymph node involvement and lymphatic vascular invasion, with sensitivities of 93 and 90%, respectively [25], especially for small tumors in predicting lymph node metastasis [26, 27]. In our study, ultrasonographic vascularity was an independent predictive factor of NSLN involvement and NSLN tumor burden, which was in agreement with previous studies.

In conclusion, our study indicated that tumor size, number of positive SLNs, mammographic mass margins, and ultrasonographic vascularity were independent predictors of NSLN metastases in SLN-positive breast cancer. Furthermore, the number of positive SLNs and ultrasonographic vascularity could also predict the tumor burden in NSLN. These results support the development of new nomograms including mammographic mass margins and ultrasonographic vascularity to increase predictive accuracy.

The limitations of this study include the small sample size and the retrospective design of the study. However, the conclusions of the present study are useful when planning additional studies. Future prospective studies in a larger patient cohort are needed to validate our findings.

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Statement of Ethics

The protocol was approved by the Hospital Human Ethical Committee (201521). Informed consent had been obtained from all patients before surgery and specimen sampling were conducted.

Disclosure Statement

The authors have no conflicts to disclose.

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