Predictors of nonsentinel lymph node metastasis in patients with breast cancer with metastasis in the sentinel node

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Abstract

To predict the factors related to axillary nonsentinel lymph node (NSLN) metastasis in patients with positive sentinel lymph node (SLN) of early breast cancer.

The retrospective data are collected from the patients with positive SLN who received further completion axillary lymph node dissection (cALND) in Peking Union Medical Hospital between March 2016 and December 2017. Univariate analysis was conducted on data with various clinicopathologic factors at first. Those factors with statistic significance ($P < .05$) in univariate analysis were then used to implement multivariate analysis and logistic regression.

There were total of 734 patients who received SLN biopsy , among whom 153 cases were included in our study. About 39.22% (60/153) of 153 paitents with positive SLN had no NSLN metastasisted to SLN. Univariate analysis showed that 3 variables were significantly correlated with NSLN involvement: tumor size ($X^2 = 10.384$, $P = .001$), SLN metastasis ratio (number of positive SLNs/number of SLNs removed $\times$ 100%) ($X^2 = 10.365$, $P = .001$) and the number of negative sentinel nodes ($X^2 = 10.384$, $P = .006$). In multivariate analysis and logistic regression, tumor size (odds ratio [OR] = 3.392, 95% confidence interval [CI]: 1.409–8.166, $P = .006$) and SLN metastasis ratio (OR = 3.514, 95% CI: 1.416–8.72, $P = .007$) were the independent risk factors. While the number of negative sentinel nodes (OR = 0.211, 95% CI: 0.063–0.709, $P = .014$) was the independent protective factor. The calculated risk resulted in an area under the curve of 0.746 (95% CI: 0.644–0.848), suggesting stable discriminative capability in Chinese population.

For those patients with positive SLN, larger tumor burden and SLN metastasis ratio are independent risk factors for NSLN metastasis. However, the more of the detected negative SLN, the less possibility with NSLN involvement.

Abbreviations: ACOSOG = American College of Surgeons Oncology Group, ASCO = American Society of Clinical Oncology, AUC = the area under the curve, cALND = completion axillary lymph node dissection, EORTC = European Organization for Research and Treatment of Cancer, ER = estrogen receptor, H&E = hematoxylin and eosin, IBCSG = International Breast Cancer Study Group, MDA = MD Anderson, MSKCC = Memorial Sloan Kettering Cancer Center, NCCN = National Comprehensive Cancer Network, NSLN = nonsentinel lymph node, PR = progesterone receptor, PUMCH = Peking Union Medical College Hospital, ROC = operating characteristic curve, SLN = sentinel lymph node, SLNB = sentinel lymph node biopsy.

Keywords: breast cancer, completion axillary lymph node dissection, nonsentinel lymph node, sentinel lymph node

1. Introduction

For now, breast cancer accounts for more than 25% of cancers in women.[1] Therefore, it is the most frequently life-threatening cancer in women and the leading cause of cancer death among women worldwide. For treatment, surgery is always the main method, in which the axillary lymph node staging is of important value for evaluating the prognosis and formulating the treatment plan. Because completion axillary lymph node dissection (cALND) may lead to complications such as upper limb lymphedema, sensory numbness, and shoulder joint activity disorder, which will affect the quality of life of the patients.[2] Instead of that sentinel lymph node (SLN) biopsy has widely replaced cALND as routine axillary staging for patients with breast cancer with clinically negative axilla.[3] In addition to that, the recent study, American College of Surgeons Oncology Group (ACOSOG) Z0011 trial[4] suggested that cALND could be spared even in patients with a metastasis in SNs with sufficient adjuvant therapy including at least radiation for the patients according to the criteria (cT1-2N0M0) which could be treated with breast conserving surgery with 1 or 2 positive SNs. This new standard, now incorporated into the National Comprehensive Cancer Network's (NCCN) guidelines, was supported by ACOSOG Z0011 trial.[5] Furthermore, for the European Organization for Research and Treatment of Cancer (EORTC 10981-22023 AMAROS) trial, enrolled 1425 patients with positive SLNs, there is no statistical difference between the 2 groups. One group received ALND, and the other received axillary radiotherapy only. Based on the trial, even if SLN was positive, it could be replaced by axillary radiotherapy instead of cALND.[6] Still, The

International Breast Cancer Study Group (IBCSG) 23-01[7] trial focused on whether carrying out cALND or not will affect the survival of the patients with sentinel node micrometastasis. As a result, the experiment showed that the patients with SLN as micrometastases or isolated tumor cells did not need to be treated.

As far as we know, for approximate 50% to 65% patients, the SLN is the sole site of regional node metastasis.[8–12] And recent new data found many patients with positive SLNs undergoing cALND, which seemed to lack non-SLN (NSLN) involvement.[13] Therefore, if we can pick out those patients with only SLNs metastasis, it is possible to avoid unnecessary axillary lymph node dissection in this subgroup. There are a number of nomograms for predicting NSLN status in patients with positive SLNs, such as Memorial Sloan Kettering Cancer Center (MSKCC), Mayo, MD Anderson (MDA), Tenon, and Stanford.[14] In this study, we try to identify the clinicopathologic characteristics from the patients with SLN metastasis in our hospital that may reliably predict which patients with SLN metastasis have a low likelihood of NSLN involvement[15] and may not benefit from cALND.

2. Materials and methods

2.1. Subjects
2.1.1. Peking Union Medical College Hospital patient series.
Retrospective data of 734 consecutive patients with a primary operable lymph node negative breast cancer who underwent a SLN biopsy at the Peking Union Medical College Hospital (PUMCH) between March 2016 and December 2017 was collected from PUMCH Breast Center database. The inclusion criteria included: invasive breast cancer of cT1–T2; The axilla was considered negative by clinical examination and ultrasound (cN0); Micro- or macrometastasis of SLN by pathologic diagnosis; cALND had been performed. The exclusion criteria included: local recurrence or systemic metastasis at the initial diagnosis; inflammatory breast cancer; patients who received neo-adjuvant chemotherapy or radiotherapy; patients who received SLNB only without further cALND. Among those who received SLNB, 203 cases had SLN involvement. In consideration of patients' desire, 47 patients did not proceed to axillary clearance. As a result, 156 patients were included in our study who underwent SLN biopsy followed by cALND according to the criteria of micro- or macrometastasis in SLN biopsy. Complete data were available for patients (Fig. 1).

2.1.2. Data collection.
All data were collected including age, operation, pathologic type, tumor size, tumor differentiation, estrogen receptor (ER) status, progesterone receptor (PR) status, Her-2 status, Ki-67 index, molecular subtypes, lymph-vascular invasion (LVI), multifocal, number of SLN removed, number of positive SLNs, number of negative SLNs, SLN metastasis ratio, micro- or macrometastasis of SLN, tumor position, and distance of tumor to the nipple.

2.2. Methods
2.2.1. Location of SLN.
The location of SLN was performed using a combination of indocyanine green and blue dyes. If the tumor was not resected before SLNB, indocyanine green would
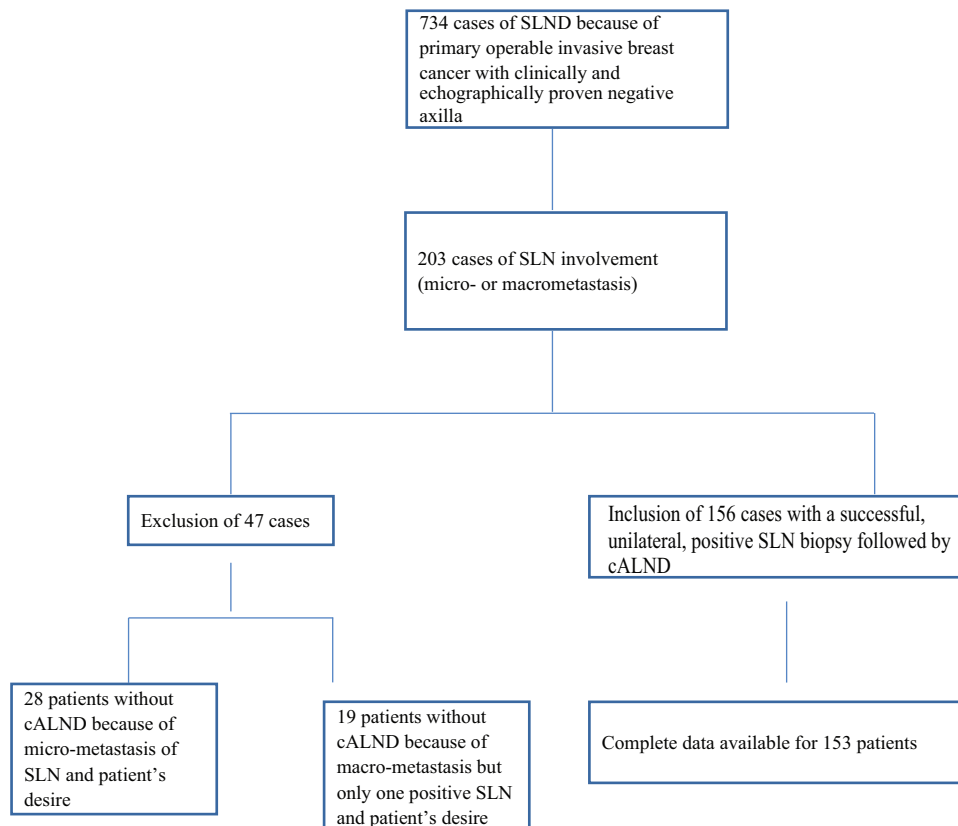

Figure 1. Patient selection and collection of data for Peking Union Medical College Hospital patient series. About 203 patients with sentinel lymph node involment from the retrospective database in whom 156 meet the inclusion standard. At last 153 cases are eligible to be enrolled in the study.

be injected at 4 sites intradermal on the edge of the areola with total volume of 0.4 to 0.6 mL. Then 2 mL of methylene blue dye was injected at 4 sites near to where injecting indocyanine green intradermal and subcutaneous periareola. On the other case that after tumor resection, indocyanine green and methylene blue were injected intradermal and subcutaneous respectively peri-tumourally near the axillary side with the same volume. Fifteen minutes of breast massage was necessary before incision. Through the fluorescence imaging instrument, we would mark the way that the indocyanine green went through the lymphatic vessel to SLN on the skin. At the site, the incision would always be located at where lied at the beginning of the axillary fold.

2.2.2. Method of SLNB.
After induction of local anesthesia in the operating room, cutting was in order following the skin, subcutaneous tissue, and plate. Intraoperative identification of SLNs was based both on blue dye and fluorescence imaging. The SLN was defined as any blue-stained node or any node with fluorescence imaging.

After SLN removal, frozen sections were performed, and the residual tissues were stained with paraffin embedded sections and stained with hematoxylin and eosin (H&E). According to the frozen pathologic result, if positive, ALND would be performed. All axillary lymph nodes (SLN and NSLN) were examined by routine H&E staining and paraffin histopathologic examination. According to both the intraoperative frozen or postoperative paraffin pathologic results, supplementary ALND was determined whether to be performed or not.

About 153 patients with adequate data who had 1 or more positive SLNs form the basis of this study.

2.3. Statistical analysis

Analyzed variables included binary variables (operation, ER, PR, Ki-67 index, LVI, multifocal lesion, number of SLNs removed, SLN metastasis ratio (number of positive SLNs/number of SLNs removed $\times$ 100%), micro- or macrometastasis of SLN, distance from tumor to nipple) and unordered categorical variables (patient's age, tumor histology, tumor size, tumor grade, Her-2 status, molecular typing of breast cancer, number of positive SLNs, number of negative SLNs, tumor location). A micrometa-stasis was defined as a tumor deposit ≤ 2 mm and macrometa-stasis was defined > 2 mm. The relationship between positivity of NSLNs and the predictive factors was assessed using the Chi-squared test. Factors at or close to the nominal ^{a}=0:05 level in univariate analyses were entered into a stepwise logistic regression. All variables that were statistically significant in univariate analysis were used to create a multivariate model for prediction of NSLN involvement. Statistical analysis was performed with SPSS 16 software (SPSS Inc, Chicago, IL). A probability level of random difference of $P < .05$ was considered significant. For internal validation of the model, a receiver operating characteristic (ROC) curve was drawn on the basis of the sensitivity and specificity of the SLN ratio, and the area under the curve (AUC) was calculated.

3. Results

Analyses are based on the 153 patients who had SLN involvement (micro- or macrometastasis) and proceeded to cALND. The clinicopathologic characteristics in the patient series are shown in Table 1. The median size of the tumor was 2.0 cm (range 0.2 to 7.1 cm) and the median age of the patients was 48 years (range 22–73 years). Only 1 was male. The mean number of

SLNs removed per patient was 3.96 (range 1–13). However, the positive SLN was 1.5 (range 0–5), while the negative was 2.5 (range 0–10). Among those, 93 patients (93/153, 60.78%) had no further positive nodes in the axilla, but 61 (60/153, 39.22%) had additional metastasis in NSLNs upon cALND. During those patients who received cALND, the mean number of NSLNs removed per patient was 20.01 (range 4–48). While the mean number of positive NSLNs was 3.45 (range 1–16). Among those, the number of only 1 NSLN involvement patients was 23 (38.33%, 23/60), that of 2 was 18 (30.00%, 18/60), and that of 3 and above was 19 (31.67%, 19/60). The number counting for 1 to 2 SLN metastasis was 135, among those that of positive NSLNs was 48 (35.56%, 48/135). To be contrast, the number counting for SLN micrometastasis was 9 (0.2 mm < tumor deposit < 2 mm), but only 1 patient involved metastasis in NSLN with only 1 positive NSLN. There are 2 cases whose SLN involved isolated tumor metastasis (tumor posit $\leq$ 0.2 mm). Both of them have no NSLN involvement.

Factors influenced in NSLN metastasis are analyzed in Table 1. With univariate analysis, NSLN metastasis was more commonly found in patients with increasing tumor size ($P = .001$; Table 1). In addition to that the patients with NSLN metastases scored significantly higher positive SLN metastasis ratio than those without NSLN metastasis did ($P = .001$; Table 1). The number of negative sentinel nodes was significant negative predictors ($P = .006$; Table 1). However, there was no significant correlation between the NSLN metastasis and the factors such as age, operation, histologic type, tumor differentiation, ER status, PR status, Her-2 status, Ki-67 index, molecular subtypes, LVI, multifocal, number of SLN removed, number of positive SLNs, micro- or macrometastasis of SLN, tumor position, and distance of tumor to the nipple.

The factors with statistically significant difference ($P < .05$) in univariate analysis were included to multivariate logistic-regression analysis. While the clinicopathologic factors related to NSLN metastasis found by Nadeem et al[16] were also included (age, tumor size, tumor differentiation, molecular subtypes, LVI, micro- or macrometastasis of SLN). The result showed that the tumor size and SLN metastasis ratio were the independent predictive risk factors of NSLN metastasis ($P = .006$, odds ratio [OR] = 3.392; $P = .007$, OR = 3.514, respectively; Table 2). To be contrast, the number of negative SLNs was the independent predictive protective factor of NSLN metastasis ($P = .014$, OR = 0.211; Table 2).

The bootstrap method corrects for overoptimism resulting from the fact that the performance of the model (AUC) was measured from the same data set as used for building the model. The bootstrap-corrected AUC for this multivariate model takes a value of 0.746 (95% confidence interval: 0.644–0.848; Fig. 2).

4. Discussion

The SLN biopsy is evolving as the preferred technique for axillary staging in breast cancer. What is next to do when SLN is positive. In 2014, American Society of Clinical Oncology (ASCO) updated SLNB guidelines for patients with early breast cancer. What is worth our attention is that if the patients with 1 to 2 SLN metastases planning to undergo breast conserving surgery and postoperative radiotherapy do not need to undergo cALND. This recommendation comes from the clinical trial, American College of Surgeons Oncology Group (ACOSOG) Z0011.[17] Furthermore, the International Breast Cancer Study Group (IBCSG) 23-01[7] trial proves that those with micrometastasis or solitary

Table 1

Clinicopathologic characteristics of 153 patients with sentinel node metastasis who proceeded to axillary clearance, and predictors of nonsentinel node metastasis.

Variable	Number of cases (% of series)	Positive NSLNs found[*] Number	% of series	Negative NSLNs found Number	% of series	$U/\chi2$	Univariate analysis P-value
Age, yr							
<50	87 (56.86)	34	39.08	53	60.92		
>50	66 (43.14)	26	39.39	40	60.61	0.002	.969
Operation							
Lumpectomy + SLNB[†] + ALND[‡]	54 (35.29)	24	44.44	30	55.56		
Lumpectomy + SLNB + modified radical mastectomy	99 (64.71)	36	36.36	63	63.64	0.957	.328
Tumor histology							
Invasive ductal carcinoma (IDC)	141 (92.16)	58	41.13	83	58.87		
Invasive lobular carcinoma (ILC)	5 (3.27)	1	20.00	4	80.00		
Others	7 (4.57)	1	14.29	6	85.71	2.817	.244
Tumor size							
<2 cm	124 (81.04)	41	33.06	83	66.94		
>2 cm	29 (18.95)	19	65.52	10	34.48	10.384	.001
Tumor grade							
I	19 (12.42)	5	26.32	14	73.68		
II	99 (64.71)	43	43.43	56	56.57	2.422	.298
III	35 (22.87)	12	34.29	23	65.71		
ER							
+	134 (87.58)	51	38.06	83	61.94		
−	19 (12.42)	9	47.37	10	52.63	0.605	.437
PR							
+	130 (84.97)	49	37.69	81	62.31		
−	23 (15.03)	11	47.83	12	52.17	0.842	.359
Her-2 status							
−	118 (77.12)	47	39.83	71	60.17		
+	27 (17.65)	10	37.04	17	62.96	0.082	.96
Uncertain	8 (5.23)	3	37.50	5	62.50		
Ki-67 index							
<14%	39 (25.49)	16	41.03	23	58.97		
>14%	114 (74.51)	44	38.60	70	61.40	0.072	.789
Molecular typing of breast cancer							
Luminal A	33 (21.57)	13	39.39	20	60.61		
Luminal B	105 (68.62)	40	38.10	65	61.90		
Her-2 (+)	7 (4.58)	3	42.86	4	57.14	0.485	.922
Basal-like	8 (5.23)	4	50.00	4	50.00		
LVI							
Without	137 (89.54)	52	37.96	85	62.04		
With	16 (10.46)	8	50.00	8	50.00	0.872	.35
Multifocal lesion							
No	136 (88.89)	55	40.44	81	59.56		
Yes	17 (11.11)	5	29.41	12	70.59	0.771	.38
No. of SLNs removed							
<3	48 (31.37)	23	47.92	25	52.08		
>3	105 (68.63)	37	35.24	68	64.76	2.221	.136
No. of positive SLNs							
1	110 (71.90)	38	34.55	72	65.45		
2	26 (16.99)	11	42.31	15	57.69	5.745	.057
>3	17 (11.11)	11	64.71	6	35.29		
No. of negative SLNs							
0	27 (17.65)	18	66.67	9	33.33		
1	31 (20.26)	10	32.26	21	67.74	10.384	.006
>2	95 (62.09)	32	33.68	63	66.32		
SLN metastasis ratio[§]							
Not-100%	126 (82.35)	42	33.33	84	66.67		
100%	27 (17.65)	18	66.67	9	33.33	10.365	.001
Metastasis of SLN							
Micrometastasis[‖]	9 (5.88)	1	11.11	8	88.89		
Macrometastasis[¶]	144 (94.12)	59	40.97	85	59.03	3.169	.075
Tumor location							
Internal inferior quadrant	5 (3.27)	4	80.00	1	20.00		
Outer inferior quadrant	16 (10.46)	6	37.50	10	62.50	5.618	.23
Internal upper quadrant	35 (22.87)	10	28.57	25	71.43		
Upper outer quadrant	65 (42.48)	28	43.08	37	56.92		
Peri-areola	32 (20.92)	12	37.50	20	62.50		
Distance from tumor to nipple							
<1 cm	33 (21.57)	12	36.36	21	63.64		
>1 cm	120 (78.43)	48	40.00	72	60.00	0.144	.705

ALND = axillary lymph node dissection, ER = estrogen receptor, PR = progesterone receptor, LVI = lymph-vascular invasion, NSLN = nonsentinel lymph node, SLN = sentinel lymph node, SLNB = sentinel lymph node biopsy.

[*] NSLN was the abbreviation of nonsentinel node metastasis.

[†] SLBN was the abbreviation of sentinel lymph node biopsy.

[‡] ALND was the abbreviation of axillary lymph node dissection.

[§] SLN metastasis ratio = number of positive SLNs/number of SLNs removed × 100%.

[‖] A micrometastasis was defined as a tumor deposit smaller than or equal to 2 mm.

[¶] A macrometastasis was defined as a tumor deposit greater than 2 mm.

Table 2

Multivariate logistic-regression analysis testing the relationship between clinicopathologic findings and the nonsentinel lymph node metastasis.

Variable	P-value	OR	95% CI	
			Lower CI	Upper CI
Tumor size	.006	3.392	1.409	8.166
SLN metastasis ratio	.007	3.514	1.416	8.72
Age	.695	1.158	0.556	2.411
Tumor differentiation	.479	1.264	0.366	4.364
Micro- or macrometastasis of SLN	.215	0.239	0.025	2.290
Molecular subtypes	.255	0.552	0.217	1.401
Lymph-vascular invasion	.445	1.608	0.476	5.436
Number of negative SLNs	.014	0.211	0.063	0.709

CI = confidence interval, SLN = sentinel lymph node.

tumor cells of SLNs have no need to receive cALND. In addition to that the AMAROS trial[18] suggests that axillary radiotherapy is an alternative treatment to cALND for patients with early breast cancer with positive SLNB. Those 3 remind us cALND may not be the necessary operation for part of the patients with positive SLNB.

Moreover, let us focus on the complications from cALND. Long-term follow-up results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 study[3] showed that for SLNB negative patients, further ALND did not improve the survival of the patients with breast cancer but the incidence of upper limb lymphedema in the cALND was 4 times that of the SLNB patients, significantly affecting the quality of life.

Based on those 4 clinical trials, someone try to study the relationship between the clinicopathologic features and NSLN

Figure 2. Receiver operating characteristic curves for the patient series in Peking Union Medical College Hospital (PUMCH). When we evaluate the predictive value of the model for the patients from PUMCH, we obtain a bootstrap-corrected the area under the curve of 0.746.

metastases in those patients with positive SLN to reduce the incidence of complications. Kwon et al[19] included 205 patients with invasive breast cancer with at least 1 positive SLN, followed by cALND. Multivariate logistic-regression analysis showed that macrometastasis of SLN (tumor deposit > 2.0 mm), 2 and more SLNs metastasis, and extra-nodal metastasis were independent risk factors for NSLN metastasis.

In China's present clinical practice, the treatment mode from Z0011 and AMAROS trials has not been well promoted. Thus, to avoid readmissions and complications from cALND, we tried to screen those patients with low risk for positive NSLN in which cALND could safely be omitted with positive SLN. During this study, 153 patients with positive SLN have received complete axillary node dessection. Among those, 93 (93/153, 60.78%) patients had no further positive nodes in the axilla, which indicate those have no need to receive cALND in fact. Of those patients with 1 to 2 positive SLNs, the percentage of NSLN positive was accounted for 35.56% (35.56%, 48/135). Both univariate and multivariate logistic regressions showed that tumor size and SLN metastasis ratio were the independent predictive risk factors of NSLN metastasis while the number of negative SLNs was the independent predictive protective factor.

Some studies use some mathematical models to evaluate NSLN metastasis in patients with positive SLNB including 6 models such as Mayo nomograms,[20] Memorial Sloan–Kettering Cancer Center (MSKCC),[21] Tenon,[22] MDA,[23] Cambridge,[24] and Stanford[25] that have been the most widely validated in different countries.[14,26–28] Among all of them, SLN metastasis ratio is the independent predicting risk factor. In our study, the result was consistent with that of the literatures. In the MSKCC model, the high with the SLN metastasis ratio, the more likely NSLN was positive. In Tenon score, if the SLN metastasis rate <0.5, the rate of positive NSLN was only 5.9%; if the SLN metastasis rate range 0.5 to 1.0, the rate of positive NSLN ascended to 34%; if the SLN metastasis rate above 1.0, the rate of positive NSLN reached to 59 actually. While in Cambridge model, the median SLN metastasis rate was 0.5 in those patients with negative NSLN. However, there is somewhat different in this study. We divided the patients in 2 groups due to SLN metastasis rate (<100% and equal to 100%).[29] The probability of NSLN metastasis was 33.33% (42/126) in SLN+ <100% group. Compared with that the probability was 66.67% (18/27) in SLN+ equal to 100% group, nearly 2 times. Thus, SLN metastasis rate was the independent risk factor. In addition to that, the highlight in our study is the number of negative SLNs which was the independent protective factor for predicting NSLN involvement. This point has not been reported in those models above till now. The result
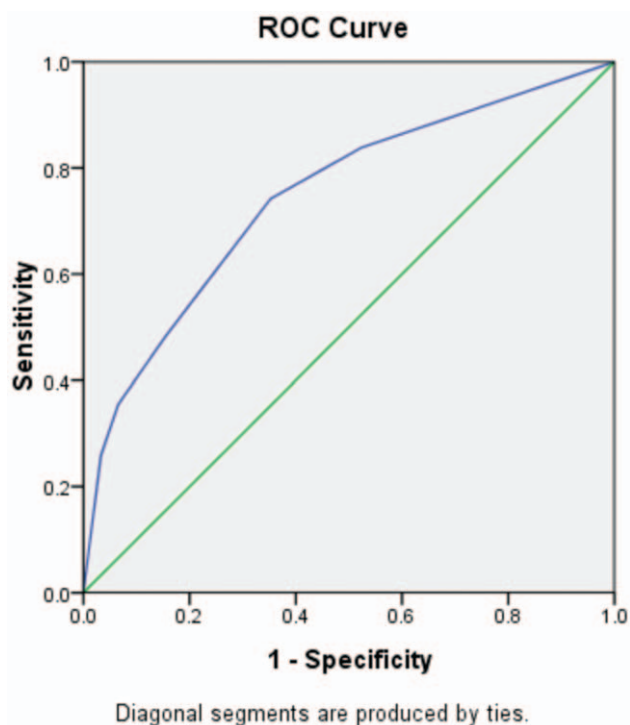
of this article is that if there is no negative sentinel node, the probability of NSLN metastasis was 66.67% (18/27), while if 1 negative sentinel node, it was 32.26% (10/31) and last if ≥2 negative sentinel nodes, that of 33.68% (32/95). The more of the number of negative SLNs, the higher probability of the negative NSLNs.

In addition to that, another independent risk factor was also found. It was tumor size. Goyal et al[30] and Noda et al[31] also reported what we found that increasing tumor burden in the SLN was associated with additional positive nodes in the axilla. Multifocal lesions might be a contraindication for SLN biopsy because of the risk of false negative and underestimation of axillary staging due to the drainage of lesions in different regions to different lymph nodes.[32] However, in our study, multifocal lesions had no statistical significance for predicting NSLN metastasis. The different result might be due to insufficient samples. Fortunately, the 3 variables we found to be predictive for NSLN involvement both in univariate and multivariate analyses, are commonly studied, and frequently found to be clinically relevant.

Due to the difference between MSKCC and our hospital, such as different population (whilte and yellow), age of onset (55–65 and 45–55 years), tracer for SLN (methylene blue and nuclide and methylene blue and indocyanine green) and different staining (H&E staining combined with immunohistochemistry staining vs H&E staining only), MSKCC model may be not suitable for Chinese population especially in PUMCH. The pooled AUCs for the Mayo, MSKCC, Tenon, MDA, Cambridge, and Stanford models were 0.728, 0.715, 0.720, 0.706, 0.721, and 0.688, respectively. In this study, the AUC value was 0.746 ($P = .000$), which performed as good as those models above, suggesting stable discriminative capability in Chinese population. Furthermore, the data from our own appear to be very important and suitable for Chinese population.

Although there are still some problems in SLNB, the application of SLNB for breast cancer will be more and more widely used. That how to identify those patients with low risk of NSLN involvement will become the research concern in the future, although the result of this study should be prospectively verified by enrolling more patients. The result from our study has reminded us some patients do not need further cALND indeed. But further studies should be conducted to identify more accurate way to find out lower risk patients for NSLN metastasis even when they had macrometastasis in SLN. The system should be simple enough to be applied clinically in various hospitals by employing routinely evaluable factors during surgery.

Furthermore, there are some limitations in this study. The AUC calculated from bootstrapping is just internal validation which may not be as much reliable as possible. It is better to have external validation. So next step for the study is to use another independent patient with breast cancer cohort to validate.

5. Conclusion

In summary, our study shows that tumors more than 2 cm and SLN metastasis ratio are independent risk factors for NSLN metastasis in patients in case of positive SLN with early breast cancers. While the number of negative SLNs more than 2 indicates less probability for NSLN involvement. Our study also emphasizes the importance of validation before introducing our any predictive model in clinic. The further research with larger sample size will be expected to construct a more reasonable model suitable for Chinese population in the future.

Author contributions

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References

[1] Chalasani P, Downey L, Stopeck AT. Caring for the breast cancer survivor: a guide for primary care physicians. Am J Med 2010;123:489–95.

[2] Ding B, Qian L, Zhao Y, et al. Meta-analysis of endoscopic axillary lymph node dissection versus conventional open excision for breast cancer [in Chinese]. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2015;40:782–9.

[3] Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010;11:927–33.

[4] Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569–75.

[5] National Comprehensive Cancer Network (NCCN). Clinical practices guidelines in oncology: breast cancer, version 2.2012. Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 20, 2012.

[6] Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15:1303–10.

[7] Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013;14:297–305.

[8] Chu KU, Turner RR, Hansen NM, et al. Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? Ann Surg 1999;229:536–41.

[9] Reynolds C, Mick R, Donohue JH, et al. Sentinel lymph node biopsy with metastasis: can axillary dissection be avoided in some patients with breast cancer. J Clin Oncol 1999;17:1720–6.

[10] Turner RR, Chu KU, Qi K, et al. Pathologic features associated with nonsentinel lymph node metastases in patients with metastatic breast carcinoma in a sentinel lymph node. Cancer 2000;89:574–81.

[11] Abdessalam SF, Zervos EE, Prasad M, et al. Predictors of positive axillary lymph nodes after sentinel lymph node biopsy in breast cancer. Am J Surg 2001;182:316–20.

[12] Weiser MR, Montgomery LL, Tan LK, et al. Lymphovascular invasion enhances the prediction of non-sentinel node metastases in breast cancer patients with positive sentinel nodes. Ann Surg Oncol 2001;8:145–9.

[13] Noguchi M. Avoidance of axillary lymph node dissection in selected patients with node-positive breast cancer. EJSO 2008;34:129–34.

[14] Zhu L, Jin L, Li S, et al. Which nomogram is best for predicting non-sentinel lymph node metastasis in breast cancer patients? A meta-analysis. Breast Cancer Res Treat 2013;137:783–95.

[15] Turner RR, Chu KU, Qi K, et al. Pathologic features associated with non-sentinel lymph node metastases in patients with metastatic breast carcinoma in a sentinel lymph node. Cancer 2000;89:574–81.

[16] Nadeem RM, Gudur LD, Saidan ZA. An independent assessment of the 7 nomograms for predicting the probability of additional axillary nodal metastases after positive sentinel lymph node biopsy in a cohort of British patients with breast cancer. Clin Breast Cancer 2014;14:272–9.

[17] Giuliano AE1, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569–75.

[18] Donker M, Slaets L, van Tienhoven G, et al. Axillary lymph node dissection versus axillary radiotherapy in patients with a positive sentinel node: the AMAROS trial [in Dutch]. Ned Tijdschr Geneeskd 2015;159: A9302.

[19] Kwon Y, Ro J, Kang HS, et al. Clinicopathological parameters and biological markers predicting non-sentinel node metastasis in sentinel node-positive breast cancer patients. Oncol Rep 2011;25:1063–71.

[20] Degnim AC, Reynolds C, Pantvaidya G, et al. Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. Am J Surg 2005;190:543–50.

[21] Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol 2003;10:1140–51.

[22] Barranger E, Coutant C, Flahault A, et al. An axilla scoring system to predict non-sentinel lymph node status in breast cancer patients with sentinel lymph node involvement. Breast Cancer Res Treat 2005;91:113–9.

[23] Hwang RF, Krishnamurthy S, Hunt KK, et al. Clinicopathologic factors predicting involvement of nonsentinel axillary nodes in women with breast cancer. Ann Surg Oncol 2003;10:248–54.

[24] Pal A, Provenzano E, Duffy SW, et al. A model for predicting non-sentinel lymph node metastaticdisease when the sentinel lymph node is positive. Br J Surg 2008;95:302–9.

[25] Kohrt HE, Olshen RA, Bermas HR, et al. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. BMC Cancer 2008;8:66.

[26] Padmanabhan N, Ayub MF, Hussain K, et al. Factors influencing non-sentinel node involvement in sentinel node positive patients and validation of MSKCC nomogram in indian breast cancer population. Indian J Surg Oncol 2015;6:337–45.

[27] Huang J, Chen X, Fei X, et al. Risk factors of non-sentinel lymph node metastasis and performance of MSKCC nomogramin breast cancer patients with metastatic sentinel lymph node [in Chinese]. Zhonghua Wai Ke Za Zhi 2015;53:941–6.

[28] Ramjeesingh R, Quan ML, Gardner S, et al. Prediction of involvement of sentinel and nonsentinel lymph nodes in a Canadian population with breast cancer. Can J Surg 2009;52:23–30.

[29] Kuo YL, Chen WC, Yao WJ, et al. Validation of Memorial Sloan-Kettering Cancer Center nomogram for predictionof non-sentinel lymph node metastasis in sentinel lymph node positive breastcancer patients an international comparison. Int J Surg 2013;11:538–43.

[30] Goyal A, Douglas-Jones A, Newcombe RG, et al. ALMANAC Trialists GroupPredictors of non-sentinel lymph node metastasis in breast cancer patients. Eur J Cancer 2004;40:1731–7.

[31] Noda S, Onoda N, Asano Y, et al. T-stage and positive sentinel nodes ratio are the useful factors to predict non-sentinel node metastasis in breast cancer patients with macro-metastasis in the sentinel node. Int J Surg 2015;14:56–60.

[32] Veronesi U, Paganelli G, Viale G, et al. Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series. J Natl Cancer Inst 1999;91:368–73.