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Preoperative Tumor Characteristics as Predictors of axillary lymph node metastasis in patients with clinical node-negative breast cancer: A Nomogram to Predict Risk

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Abstract

Objectives: This study aims to identify the risk factors for axillary lymph node metastasis (ALNM) and establish a novel nomogram for predicting the possibility of an ALNM model based on clinicopathological and characteristics of tumor location. A three-dimensional(3D) model was also established to accurately describe the location of tumors prone to axillary lymph node metastasis.

Methods: A total of 401 consecutive patients diagnosed with breast cancer in Shandong Cancer Hospital from October 2021 to February 2022 were retrospectively included and analyzed, including 313 patients in the training cohort and 88 patients in the validation cohort. Univariate and multivariate analyses were performed based on tumor location (distance from skin, chest wall, nipple and sentinel lymph node) and clinicopathological characteristics to identify the independent risk factors for ALNM. Subsequently, a novel nomogram was established to individualize the ALNM by logistic regression analysis. The nomogram was validated in a separate cohort of 88 patients from the original randomized clinical trial (the validation cohort). Finally, a 3D model was established by using the information of tumor location of patients with axillary lymph node metastasis.

Results: During the study period, 111 (35.5%) patients suffered ALNM in the training cohort and 37 (42%) patients in the validation cohort. Multivariate analysis showed six independent risk factors related to ALNM, including nuclear grade, T stage, tumor quadrant, lymphovascular invasion (LVI), distance from skin (DS), distance from nipple (DN) and distance from sentinel lymph node (DSLN). Six variables were entered into logistic regression to establish the nomogram for predicting the probability of ALNM. The nomogram of ALNM showed excellent discriminative ability and predictive accuracy. The area under the receiver operating characteristic (AUC) was 0.88 ($P<0.001$, 95%CI=0.85, 0.92) in the training cohort and 0.88 ($P<0.001$, 95%CI=0.81, 0.95) in the validation cohort. In both the training and validation cohorts, the calibration curves of the ALNM probabilities show satisfactory agreement between the ALNM predicted by the nomogram and the actual ALNM. The 3D model was successfully established and showed good results.

Conclusion: The combination of tumor location and clinicopathological characteristics can predict ALNM. Distance from tumor to skin, nipple and sentinel lymph node has been proved to be an important factor in ALNM. A novel nomogram might serve as a practical tool for ALNM. We also innovationly established a 3D model of tumor location. The constructed models could predict ALNM with good performance, which is meaningful to patient stratification and individual treatment strategies optimization.

Keywords: Three-dimensional model; Tumor location; A Novel Nomogram; Prediction Model; Axillary lymph node metastasis

Introduction

Breast cancer stills the most commonly diagnosed cancer among women in the Global Cancer Statistics 2018, with approximately 2.1 million newly diagnosed cases every year [1]. The axillary lymph node status is the most important prognostic factor in patients with early breast cancer. It is a multifactorial event determined by patients and tumor characteristics. However, 20-30% of node positive patients remain free of distant metastasis whereas 20-30% of lymph node negative patients will eventually develop metastasis [2]. Axillary lymph node dissection (ALND) could provide accurate axillary staging information, but often leads to complications such as lymphedema of the arms, shoulder restriction, upper extremity numbness, and weakness. Sentinel lymph node biopsy (SLNB) has been proved to be a minimally invasive alternative to ALND, especially for the patients with clinically negative axilla.

As reported in the American College of Surgeons Oncology Group (ACOSOG) Z0011 trail and AMAROS trial, overall survival outcome of SLNB plus whole-breast irradiation is non-inferior to that of ALND in patients with T1 and T2 tumors and one or two positive sentinel lymph nodes (SLNs). As the tendency to less-invasive axillary surgery, ALND could be omitted for patients with 1 or 2 positive SLNs [3,4].

However, SLNB is still limited for predicting ALN status because of a false-negative rate of 5% to 10% and technical failure in 2% to 6% of cases. Besides, only 24.8% to 35.5% clinically negative SLN patients have SLN metastasis in pathological results, accounting for three quarters of patients with excessive surgery. Three ongoing prospective European trials (SOUND, INSEMA, BOOG 2013-08) compared SLNB with axillary observation only in patients with clinical lymph node negative (cN0) and primary breast conserving surgery. The purpose was to evaluate the oncologic safety when SLNB was omitted. Therefore, accurate preoperative prediction of ALN status is urgently needed.

Two nomograms were established using a variety of clinicopathological factors, including age, tumor size, histology, upper inner quadrant or not, multifocality, lymphovascular invasion, biologic subtype, to predict ALN positivity by Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center, respectively. The latter study demonstrated that body mass index (BMI), distance from skin (DS) and nipple (DN) and so on are also related to ALN metastasis. Despite these factors and tests, predicting patient outcome is not truly enough, as patients with similar pathological characteristics treated with identical regimens often exhibit highly variable clinical outcomes, indicating that additional prognostic factors are still need to be identified to improve patient stratification. However, there are no nomograms to update to take these predictive variables into consideration.

Therefore, in this study, the tumor is placed in a three-dimensional(3D) spatial position by using the tumor quadrant and the distance from the tumor to the skin, chest wall, nipple and SLNs. And combined with clinical factors to explore the effect of tumor location on axillary lymph node status in cN0 patients. Based on these factors, we established a novel predictive nomogram and 3D model to evaluate the probability of ALNM for cN0 patients.

Material and Methods

Study population

From October 2021 to February 2022, a consecutive cohort of patients with newly diagnosed, clinically T1 and T2 breast cancers with negative axilla (no suspicious LNs on either physical examination or imaging) were reviewed in the Shandong Cancer Hospital and Institute (Shandong, P.R. China). Eligibility criteria were:

1. Available clinic pathological and ultrasonographic data.
2. Surgical staging within 2 months of breast ultrasonography.
3. No treatment and biopsy were performed between ultrasound and axillary surgery, to avoid its effect to axillary status.
4. No receive neoadjuvant chemotherapy.
5. No prior history of breast cancer.

A total of 401 breast cancer patients were included for analysis. The screening process shown in Figure 1. The study was approved by the institutional review committee of Shandong cancer hospital. All patients signed informed consent.

Abstraction clinicopathological and ultrasonographic data

The clinical and demographic data of patients were from the clinical medical records. The pre-surgery ultrasonography examinations were performed with a dedicated breast ultrasound system (Phillips iU22 Ultrasound System, Bothell, WA) using high-frequency (12.5 and 17.5 MHz) linear array transducers by an experienced sonographer. For ultrasonic evaluation of lymph nodes and tumors, we use the long axis method (Figure 1A). Ultrasonography parameters such as tumor size, tumor locations, and distance from nipple (DN) was collected. distance from skin (DS), distance from chest wall (DCW) and distance from sentinel lymph node (DSLN) were not routine terms but were used in our ultrasound department. DN and DCW were defined as the distance from the skin surface and the chest wall surface to the closest edge of the tumor respectively. DN was defined as the distance from the skin marker of the tumor epicenter to the epicenter of the nipple. Most frequent location of the SLNs was the area demarcated by the four landmarks of the hairline, a line tangential to and 2 cm below the center of the hairline, the lateral border of the pectoralis major muscle, and the mid-axillary line, accounting for 98.4% of patients (Figure 1B). DSLN was defined as the distance the center of above-mentioned area to the skin marker of the tumor epicenter. (For patients with multiple masses on US, the largest mass was evaluated in each patient.). According to the geometric method, the breast is divided into four quadrants: upper outer quadrant (UOQ), lower outer quadrant (LOQ), upper inner quadrant (UIQ), lower inner quadrant (LIQ) and central portion.

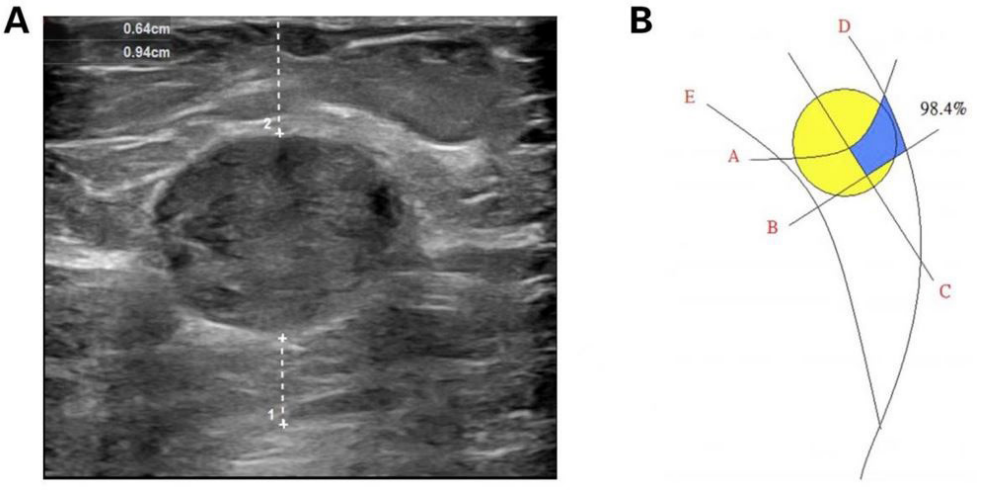

Figure 1: A. Ultrasound measures the vertical distance from the upper and lower edges of the tumor to the skin and chest wall.
B. Comparison of this area (yellow) with the smaller area containing 98.4% of SLNs determined in our study (blue)

Primary tumors and LNs were staged according to the 8th edition of the American Joint Committee on Cancer staging system. ER and PR status were considered positive if more than 1% of the tumor cells showed the immunohistochemical stain. HER-2 status was considered positive if the immunohistochemical stain was 3+ or 2+ with confirmation of HER-2 gene amplification by fluorescence in situ hybridization (PathVysion HER-2 DNA Probe Kit; Abbott Laboratories, Chicago, IL, USA).

The tumor characteristics, including age, T stage, nuclear grade, pathological subtypes, LVI, number of foci, tumor location, palpable, DS, DN DCW, DSLN, immunohistochemical status and axillary staging, were abstracted from ultrasonography and pathology reports.

Sentinel lymph node detection technique

SLNB was performed at our institution by the seasoned surgeons with dual tracer (99mTc-labeled sulfur colloid and methylene dye). The sulfur colloid was filtered through a millipore filter with a pore diameter of 220 nm (Beijing Atomic Galactic Jinan Drug Center, Beijing, China) and labeled with 99mTc. About 2 hours before operation, 18-37 MBq of 99mTc labeled sulfur colloid was injected into the breast parenchyma around the areola. Lymph scintigraphy was obtained before operation (Philips Electronic N.V, Beijing, China). Methylene blue (2–4 mL) was injected subcutaneously surrounding the areola and tumor 10 min before the SLNs tracing. SLNs were identified as blue-stained nodes and radioactive nodes, measured with a gamma probe (Navigator, US Surgical). The skin markers of SLNs were confirmed using a point source matched technique by the preoperative lymphoscintigraphy. A standard Level I and II node dissection was performed to avoid missing "skip" metastases in all patients.

Decision prediction nomograms and validation

A novel nomogram for ALNM was created based on the multivariable logistic regression model ($P<0.05$). Finally, the ROC curve was drawn to evaluate the accuracy of the prediction model, which ranges from 0.5 (random) to 1.0 (perfect). The Y-axis of the calibration curve represents the actual observed survival rate, and the X-axis represents the survival rate predicted by the established nomogram in the training cohort and validation cohort. Finally, in order to further confirm the accuracy of the conclusion, we used the confidence interval(95%CI) of odds ratio to establish a forest plot. As long as the horizontal line does not intersect with the vertical line of $x = 1$, it proves that this factor is statistically significant. When the horizontal line is completely on the left of $x = 1$, this factor is a protective factor. If the horizontal line is completely to the right of $x = 1$, this factor is a risk factor.

Establishment of 3D model

Through the tumor quadrant, the distance from the tumor to the skin, chest wall, nipple and SLNs, the accurate position of the tumor in the 3D space was determined. The x-axis represents DN, the y-axis represents DSLN, and the z-axis represents DS, The breast area prone to axillary lymph node metastasis has a greater density in the 3D space.

Statistical analysis

All statistical data were analyzed by SPSS version 26.0 (SPSS company, Chicago, Illinois, USA) and R 4.0.3 (The R Project for Statistical Computing, www.r-project.org). Continuous data were summarized using the mean ± SD. Categorical variables were compared using Fisher exact test or the chi-square test. Univariate and multivariate logistic regression analyses were performed using a input selection of all factors studied as candidate predictors of ALNM. A two-sided P value of <0.05 was considered statistically significant.

Results

Clinicopathological characteristics

During the October 2021 to February 2022, 313 patients were diagnosed clinically T1 and T2 breast cancers with negative axilla in the training cohort and 88 patients were included in the validation cohort (Figure 1). The baseline clinicopathological characteristics in the training cohort and the validation cohort were shown in Table 1. In the training cohort, the median age at diagnosis was 50 years (range, 20 to 85 years). A total of nuclear grade I, II, III were 15(4.7%), 184(58.7%), 114(36.4%) patients respectively. The clinic diagnosed 181(57.8%) patients with T1 and 132(42.1%) patients with T2. The main tumor type was invasive ductal carcinoma (85.9%). Among the tumor location of all patients, UOQ accounted for the highest proportion (32.9%), and UIQ, LIQ, LOQ and Central portion accounted for relatively low proportions (8.9%, 29.0%, 26.1%, and 2.8% respectively). After obtaining the pathological results, we observed 111 ALNM events in the training cohort, whose estimated was 35.5%. Among the 111 patients with ALNM, 62(55.8%) had metastasis with lymphovascular invasion and 77(69.3%) with unifocal. In the validation cohort, most of the data are similar to the training set. It was worth noting that the mean and median of DN, DS, DCW and DSLN in the verification set are slightly smaller than the training set.

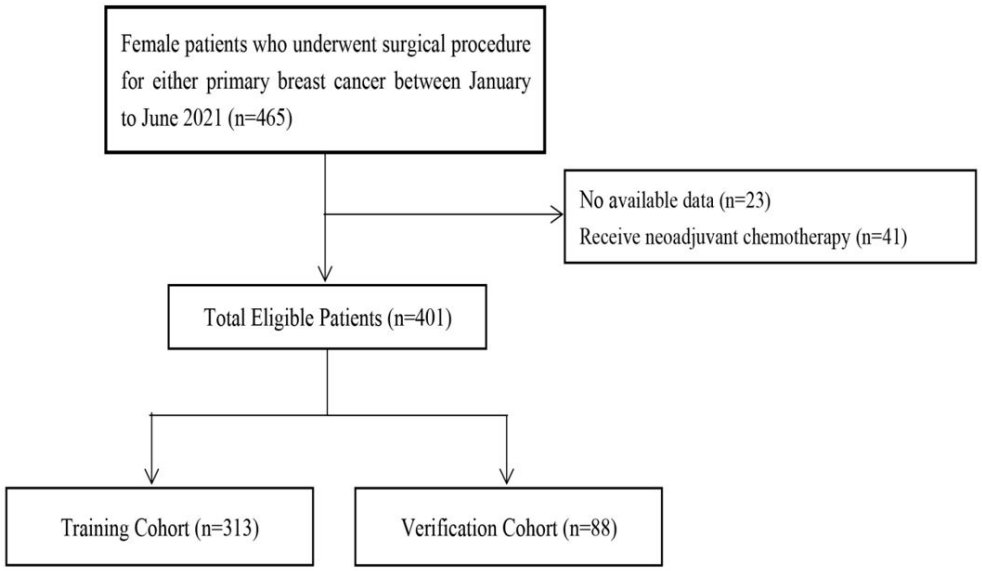

Figure 2: Consort diagram for the study cohort.

Table 1: The basic information, clinicopathological and tumor distance characteristics of the training cohort and validation cohort.

Characteristic	Training cohort		Validation cohort	
	Total (%)	ALNM (%)	Total (%)	ALNM (%)
Age				
<50	137(43.8)	44(39.6)	38(43.2)	14(37.8)
≥50	176(56.2)	67(60.4)	50(56.8)	23(62.2)
BMI				
≤24kg/m^2	194(62.0)	64(57.7)	57(64.8)	22(59.5)
>24kg/m^2	119(38.0)	47(42.3)	31(35.2)	15(40.5)
Nuclear grade				
I	34(10.8)	5(4.5)	9(10.2)	3(8.1)
II	155(49.5)	49(44.1)	44(50.0)	10(27.0)
III	124(39.6)	57(51.3)	35(39.7)	24(64.8)
T stage				
T1	187(59.7)	58(52.2)	48(54.5)	22(59.4)

T2	142(45.3)	53(47.7)	40(45.5)	15(40.5)
Pathological subtypes				
IDC	269(85.9)	93(83.7)	72(81.8)	31(83.7)
ILC	29(9.2)	13(11.7)	14(15.9)	5(13.5)
Others	15(4.7)	5(4.5)	2(2.2)	1(2.7)
Tumor quadrant				
UIQ	29(9.2)	3(2.7)	10(11.3)	1(2.7)
LIQ	86(27.4)	12(10.8)	21(23.8)	4(10.8)
UOQ	103(32.9)	59(53.1)	36(40.9)	21(56.7)
LOQ	86(27.4)	32(28.8)	17(19.3)	9(24.3)
Central portion	9(2.8)	5(4.5)	4(4.5)	2(5.4)
Breast diameter				
≤15cm	212(67.7)	75(67.6)	58(65.9)	25(67.6)
>15cm	101(32.3)	36(32.4)	30(34.1)	12(32.4)
Palpable				
Yes	268(85.6)	97(87.3)	59(67.0)	27(72.9)
No	45(14.3)	14(12.6)	29(32.9)	10(27.1)
ER status				
Positive	228(72.8)	74(66.6)	71(80.6)	32(86.4)
Negitive	85(27.1)	37(33.3)	17(19.3)	5(13.5)
PR status				
Positive	222(70.9)	79(71.1)	73(82.9)	30(81.0)
Negitive	91(29.1)	32(28.8)	15(17.0)	7(18.9)
HER-2 status				
Positive	93(29.7)	34(30.6)	23(26.1)	10(27.0)
Negitive	220(70.2)	77(69.3)	65(73.8)	27(72.9)
LVI				
Yes	124(39.6)	65(58.5)	32(36.3)	21(56.7)
No	189(60.3)	46(41.4)	56(63.6)	16(43.2)
Number of foci				
Unifocal	242(77.3)	80(72.0)	72(81.8)	27(72.9)
Multifocal	71(22.6)	31(27.9)	16(18.1)	10(27.1)
DN				
Mean (±SD)	5.9(2.05)	4.97(1.87)	4.69(1.34)	4.32(1.17)
Min, median, max	1.2, 5.7, 12.7	1.2,4.8,10.5	1.2, 4.75,8.5	1.2,4.6,6.4
DS				
Mean (±SD)	1.24(0.57)	0.95(0.50)	1.22(0.56)	0.99(0.50)
Min, median, max	0.13, 1.32,2.8	0.13,0.76,2.18	0.19,1.2,2.36	0.19,0.87,2.02
DCW				
Mean (±SD)	1.1(0.47)	1.04(0.44)	1.04(0.50)	1.13(0.51)
Min, median, max	0.16,1.15,1.98	0.21,1.15,1.86	0.13,1.13,1.89	0.13,1.15,1.89
DSLN				
Mean (±SD)	8.9(2.35)	7.84(2.16)	9.14(2.41)	7.92(1.90)
Min, median, max	2.1,8.9,16.8	2.1,7.7,13.2	5.3,8.8,14.7	5.5,7.2,12.1

ALNM, axillary lymph node metastasis; BMI,body mass index; IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma; UIQ, upper inner quadrant; LIQ, lower inner quadrant; UOQ, upper outer quadrant; LOQ, lower outer quadrant; ER, Estrogen receptor; PR, Progesterone receptor; Her-2, Human epidermal growth factor receptor-2; LVI, Lymphovascular invasion; DS, Distance from tumor to skin; DN, Distance from tumor to nipple; DCW, Distance from tumor to chest wall; DSLN, Distance from tumor to sentinel lymph node

Univariate and Multivariate Survival Analysis

Table 2 presents the univariate and multivariable analysis, which identified the following factors associated with ALNM: nuclear grade, T stage, tumor quadrant, palpable, LVI, number of foci, DN, DS, DCW, and DSLN. The results show that after considering multiple factors, nuclear classification is the predictor of ALNM. Compared with nuclear grade I, nuclear grade II (p=0.022, OR [95% CI]=4.37 [1.24-15.43]) and III (p=0.001, OR [95% CI]=9.80 [2.68-35.76]) showed significant differences.

In the tumor location, UOQ showed a significal results (p=0.011, OR [95% CI]=7.43 [1.58-34.90]), In the distance of index, DS (p<0.001, OR [95% CI]=0.19 [0.1-0.36]), DN (p<0.001, OR [95% CI]=0.63 [0.52-0.76]) and DSLN (p=0.022, OR [95% CI]=0.80 [0.66-0.97]). Significantly, although the T stage was independent risk indicators in univariate analysis, it did not show significant difference in multivariate analysis (p=0.912, OR [95% CI]=0.96 [0.50-1.87]).

Table 2: Univariate and multivariate logistic regression analysis of ALNM from the training cohort

Factors	Univariate		Multivariate
	P-value	OR (95%CI)	P-value
Age of onset	0.387		
BMI			
≤24kg/m^2	Ref		
>24kg/m^2	0.537		
Nuclear grade			
I	Ref		
II	0.055	4.37(1.24-15.43)	0.022
III	0.002	9.80(2.68-35.76)	0.001
T stage			
T1	Ref		
T2	0.046	0.96(0.50-1.87)	0.912
Pathological subtypes			
IDC	Ref		
ILC	0.276		
Others	0.922		
Palpable			
No	Ref		
Yes	0.510		
ER status			
Positive	Ref		
Negitive	0.070		
PR status			
Positive	Ref		
Negitive	0.944		
HER-2 status			
Positive	Ref		
Negitive	0.792		
Number of foci			
Unifocal	Ref		
Multifocal	0.102		

Tumor quadrant			
UIQ	Ref		
LIQ	0.619	1.75(0.35-8.68)	0.493
UOQ	<0.001	7.43(1.58-34.90)	0.011
LOQ	0.012	3.22(0.70-14.85)	0.133
Central portion	0.009	0.87(0.11-7.18)	0.899
Breast diameter			
≤15cm	Ref		
>15cm	0.195		
LVI			
No	Ref		
Yes	<0.001	2.92(1.53-5.55)	0.001
DS	<0.001	0.19(0.10-0.36)	<0.001
DCW	0.121		
DN	<0.001	0.63(0.52-0.76)	<0.001
DSLN	<0.001	0.80(0.66-0.97)	0.022

ALNM, axillary lymph node metastasis; OR, Odds ratio; CI, confidence interval; Ref, Reference; BMI,body mass index; IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma; UIQ, upper inner quadrant; LIQ, lower inner quadrant; UOQ, upper outer quadrant; LOQ, lower outer quadrant; ER, Estrogen receptor; PR, Progesterone receptor; Her-2, Human epidermal growth factor receptor-2; LVI, Lymphovascular invasion; DS, Distance from tumor to skin; DN, Distance from tumor to nipple; DCW, Distance from tumor to chest wall; DSLN, Distance from tumor to sentinel lymph node

Prediction Model of the ALNM Nomogram

After univariate and multivariate analyses, based on the above the independent predictive indicators, the meaningful clinicopathological characteristics in multivariate analysis were combined to construct the prediction model. The dependent variable was the incidence of ALNM. After entering binary logistic regression, it was determined that DSLN was the best predictor. Nuclear grade, Tumor location, LVI, DS, DN, DSLN were integrated and demonstrated using a novel nomogram (Figure 3). According to the weight of the independent variable in the regression model, the score of the nomogram was given. The scale length of the nomogram variables was positively correlated with their influence on the efficacy prediction. The area under the curve represents the distribution of each set of data. Among all factors, DSLN contributed the most to the prediction results and the peak appeared in the region of 9-10 cm. This was followed by DN, DS, nuclear grade, LVI and tumor location. In DSLN, the high-risk segment corresponds to the high partition (scoring axis), and the low-risk segment corresponds to the low partition. Add the scores of all factors to obtain the total score perpendicular to the risk axis of ALNM, and obtain the final risk of individual ALNM.

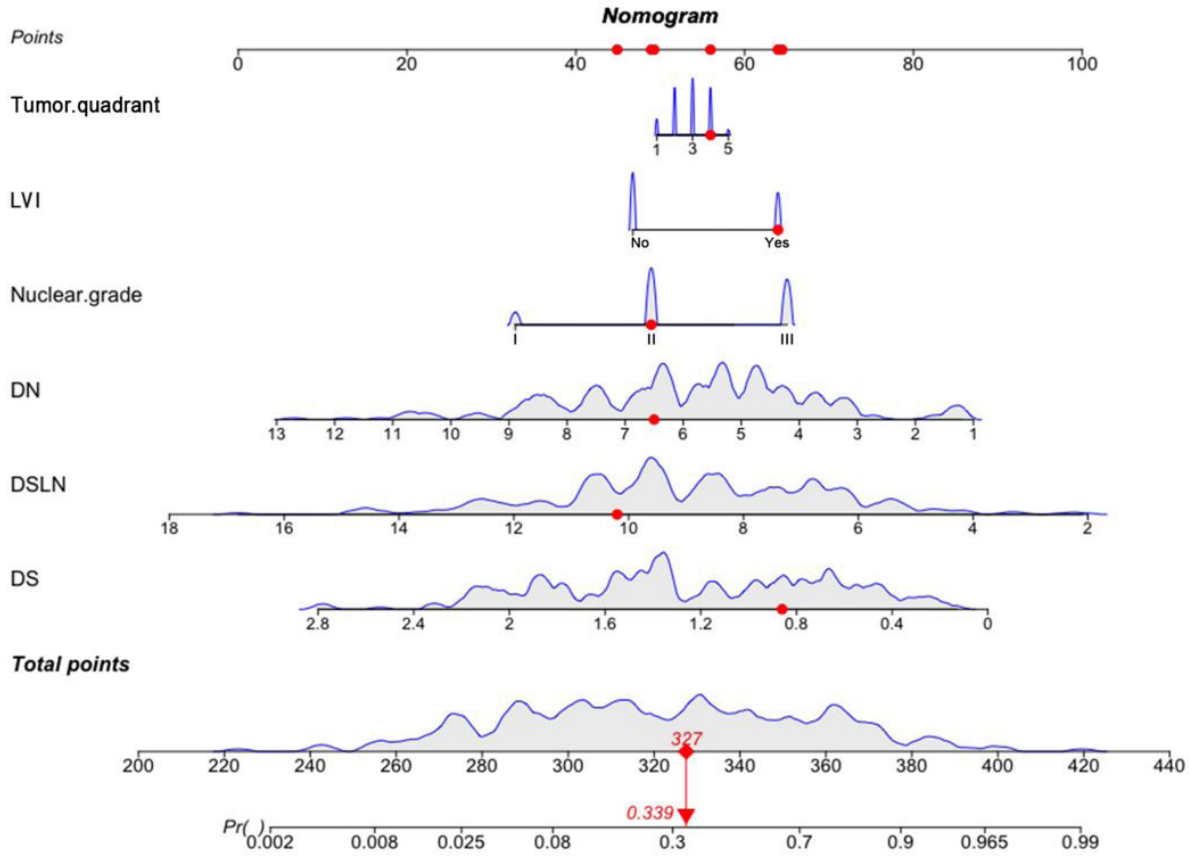

Figure 3: Nomogram model predicts the probability of axillary lymph node metastasis. Points refers to point for the individual risk factor and add together to the total points. LVI, Lymphovascular invasion; DS, Distance from tumor to skin; DN, Distance from tumor to nipple; DSLN, Distance from tumor to sentinel lymph node

To apply the nomogram, we first draw a vertical line up from the corresponding point of each variable to obtain the corresponding score and then add up the scores of each variable and draw a vertical line down from the total score row to get the probability of benefit from ALNM. For example, if a patient with UOQ, LVI, nuclear grade II, DN(6-7cm), DSLN(10-11cm) and DS(0.8-0.9cm), she will have a total score of 327, corresponding to an OR value of 0.339 (<1), indicating that she may be the high risk groups. To conclude that a schematic diagram of clinical management of suspected lymph node positive breast cancer patients based on the nomogram is illustrated (Figure 4). Once patients suspected of ALNM come to clinic, the nomogram could stratify these patients into low-risk or high-risk groups and provide prior treatment strategies for them. The novel nomogram is expected to be an effective screening tool for quantifying surgical benefit in female patients with the breast cancer, which may help oncologists make clinical decisions.

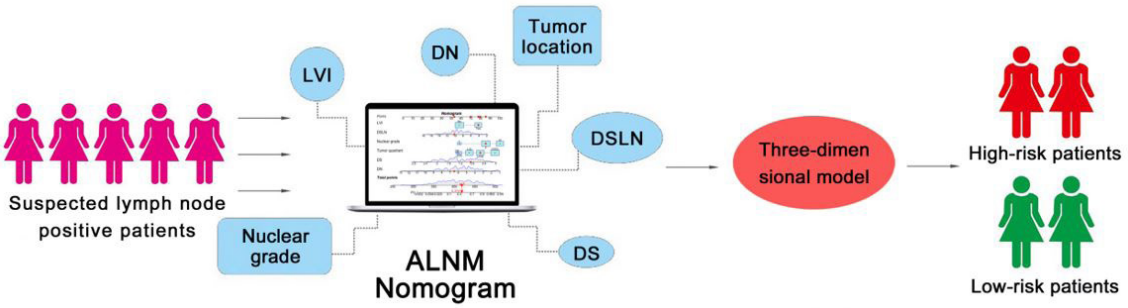

Figure 4: Clinical management of axillary lymph node metastasis breast cancer patients. The schematic diagram of axillary lymph node metastasis breast cancer patient management based on the nomogram. LVI, Lymphovascular invasion; DS, Distance from tumor to skin; DN, Distance from tumor to nipple; DSLN, Distance from tumor to sentinel lymph node

The nomogram of ALNM showed excellent discriminative ability and predictive accuracy. Calibration curves for the ALNM probability in the training and validation cohort both demonstrated satisfactory consistency between the nomogram-predicted and actual ALNM (Figure 5A,B). The area under the ROC (AUC) was 0.88 (P < 0.001, 95% CI=0.85, 0.92) in the training cohort (Figure 5C) and 0.86 (P<0.001, 95%CI=0.77, 0.96) in the validation cohort (Figure 5D).

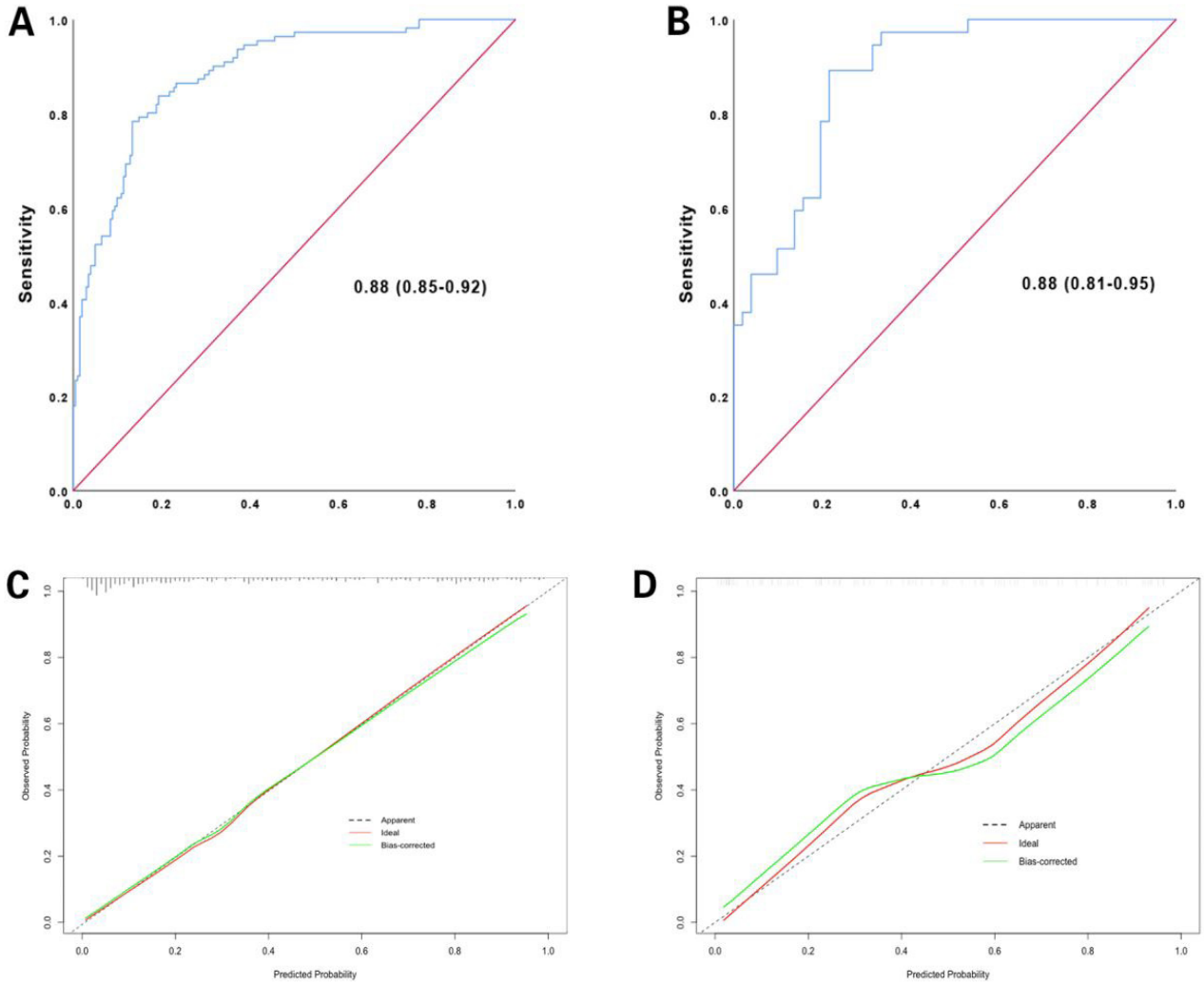

Figure 5: Evaluation of the ALNM nomogram (A-D).

The discrimination assessed by ROC curves for the nomogram in the training cohort (A) and validation cohort (B). The AUCs for ALNM prediction were 0.88 (95%CI=0.85, 0.92) in the training and 0.88 (95%CI=0.81, 0.95) in the validation cohort. Calibration curves for the nomogram in the training cohort (C) and validation cohort (D).

ALNM, axillary lymph node metastasis; ROC, receiver operating characteristic; AUC, area under curve.

The forest plot of the multivariable odds ratios for all factors

Figure 6 and Table 3 showed the ROC and the cut-off values of DS, DN, DSLN of patients with breast cancer in the training cohort. Combined with nomogram, it can divide all patients into high-risk and low-risk groups, and help build the next forest plot.

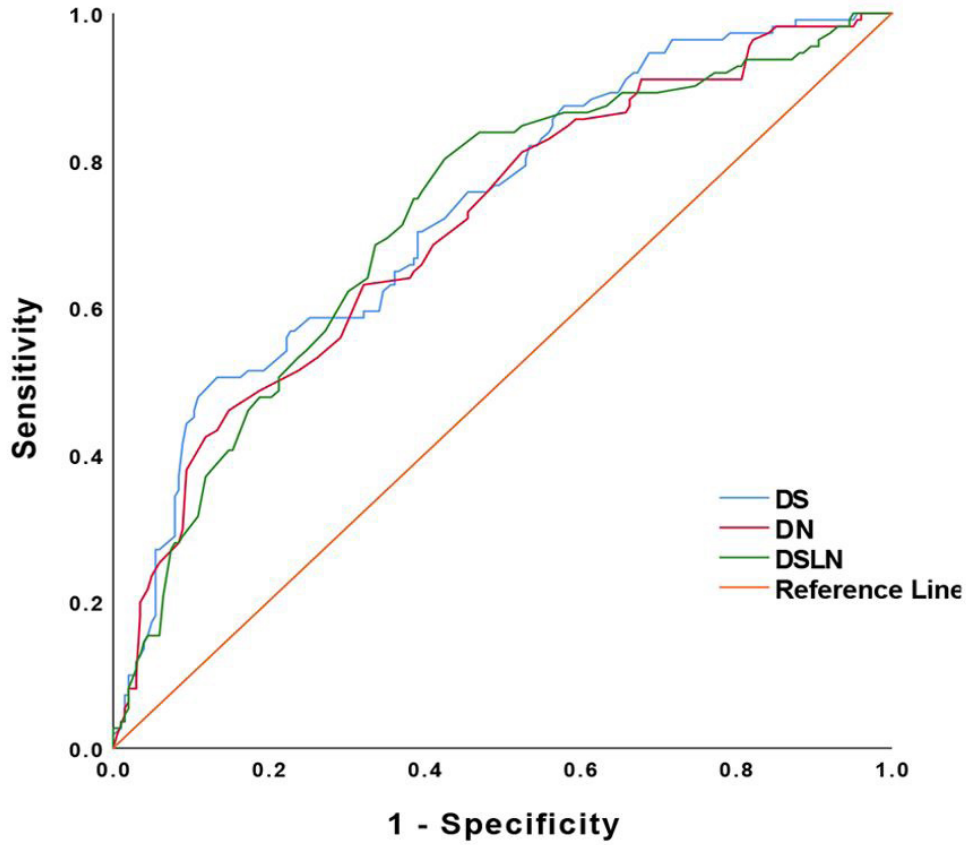

Figure 6: Optimal cut-off points for DS, DN and DSLN were on with ROC curves. ROC, receiver operating characteristic; DS, Distance from tumor to skin; DN, Distance from tumor to nipple; DSLN, Distance from tumor to sentinel lymph node

Table 3: The optimal cut-off point for ALNM

Variables	AUC	Cut-off point	P-value
DS	0.732	0.765	<0.001
DN	0.710	4.650	<0.001
DSLN	0.719	9.450	<0.001

ALNM, axillary lymph node metastasis; AUC, area under curve; DS, Distance from tumor to skin; DN, Distance from tumor to nipple; DSLN, Distance from tumor to sentinel lymph node

(Figure 7) showed a forest plot of the multivariable odds ratios for all factors. Multivariate analysis adjusting for these variables found that the association of tumor location remained significant, with the largest effects for DSLN with odds ratio of 0.431 (95% CI 0.150–0.773), followed by DN (OR 0.169, 95% CI 0.081–0.354), DS (OR 0.147, 95% CI 0.072–0.297), LVI (OR 3.240, 95% CI 1.697–6.186), nuclear grade III (OR 6.818, 95% CI 1.854–25.072) and UOQ (OR 10.509, 95% CI 2.193–50.356).

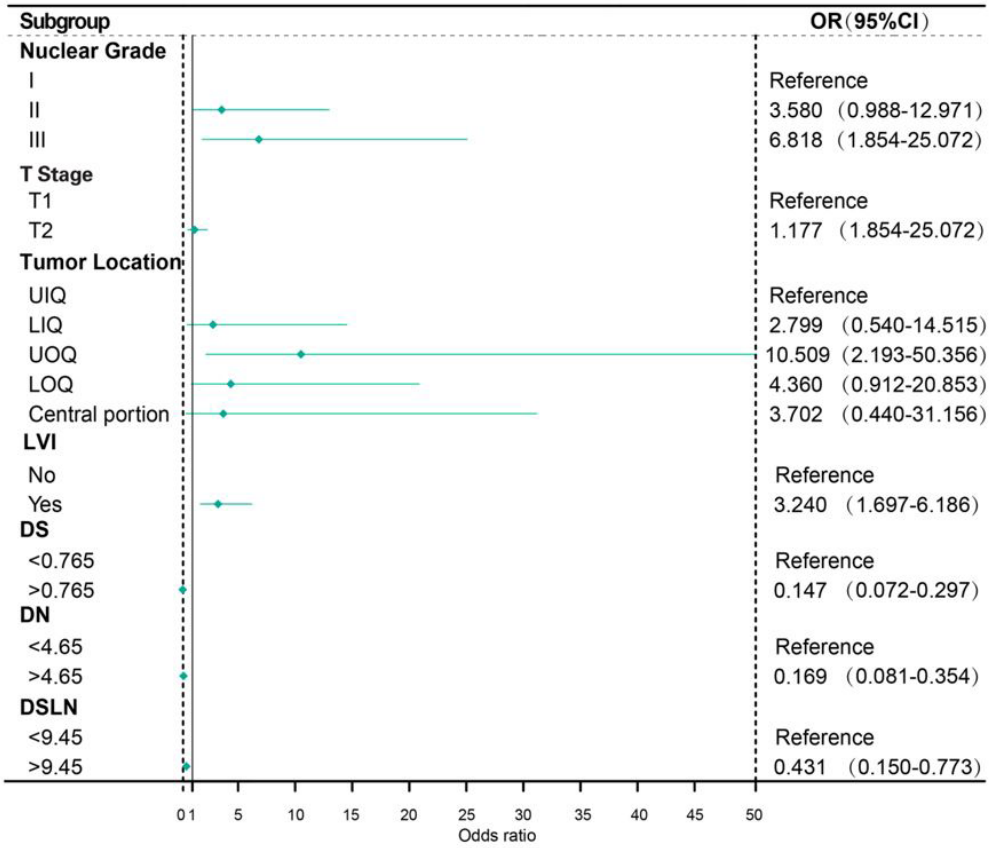

Figure 7: Multivariable analysis demonstrating effect of clinicopathological and tumor distance characteristics on axillary lymph node metastasis among cN0 breast cancer patients OR, Odds ratio; CI, confidence interval; UIQ, upper inner quadrant; LIQ, lower inner quadrant; UOQ, upper outer quadrant; LOQ, lower outer quadrant; LVI, Lymphovascular invasion; DS, Distance from tumor to skin; DN, Distance from tumor to nipple; DSLN, Distance from tumor to sentinel lymph node

3D Model of the ALNM

In the logistic regression results, the tumor quadrant was an independent risk factor for ALNM, and OUQ was more prone to metastasis. Therefore, we established a 3D model of the OUQ (taking the 3D model as the OUQ of the breast) (Figure 8). The results showed that in the 3D model, the areas with x = 6-9 cm, y = 2-6 cm and z = 1-1.5 cm had the highest density, indicating that the probability of ALNM is higher in this area.

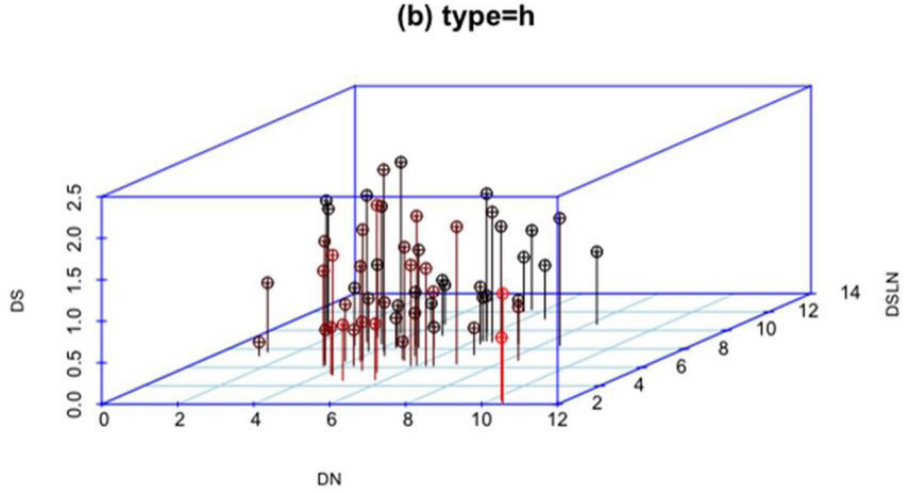

Figure 8: The 3-D model as the OUQ of the breast to prediction of axillary lymph node metastasis 3-D, three-dimensional; OUQ, upper outer quadrant

Discussion

Of the 313 breast cancer patients studied in our training cohort, 111 patients had ALNM, which was consistent with the reported range of onset (33.2%-39%) [5, 6]. After adjusting multivariate analysis, we found that tumor location, LVI, nuclear grade, DN, DS and DSLN were related to ALNM, which was roughly consistent with previous studies [7,8]. LVI was considered to be the strongest independent predictor of lymph node involvement [9, 10, 11], Our current study confirmed this finding. In our patients with lymph node metastasis, 58.5% were accompanied by LVI. Woo et al. found that LVI was still associated with a significant reduction in survival over 12 years of follow-up, even without lymph node disease, and predicted a worse prognosis in patients with lymph node disease [12]. According to the grade standard of WHO, nuclear grade was mainly divided according to the nuclear pleomorphism. Studies have shown that high LVI is associated with high nuclear and histological grade, ER and PR negative, HER2 positive, high Ki-67 proliferation index and larger tumor [13]. The study confirmed that nuclear grades II and III were significantly correlated with ALNM, but This study confirmed that nuclear grades II and III were significantly correlated with ALNM, but ER, PR and HER-2 did not show correlation with ALNM. Therefore, it can be explained that nuclear grade affected ALNM by affecting the invasion of lymphovascular. But the effects of ER, PR and HER-2 on lymph node status were not significant.

The study showed that tumor location in the breast was significantly related to ALNM, and the metastasis rate of tumors distributed in different regions of the breast was different. The study was consistent with the results of other studies, that is, the OUQ was the most common quadrant of breast tumors [14, 15], and DSLN was also an independent risk factor for ALNM in multivariate analysis.

Chen studied the direction of lymphovascular metastasis of malignant tumors in different positions of the breast by radionuclide tracing technology. The results showed that 82.4% of the tumors in the OUQ drained to the axillary lymph nodes and 8.3% to the internal mammary lymph nodes; 25% of the tumors in the medial quadrant drained into the internal mammary lymph nodes.[16] The concealment of internal mammary metastasis and the difficulty of physical and imaging examination lead to underestimation and insufficient treatment. This was also one of the reasons for the worse prognosis of internal mammary lymph node metastasis [17].

As we all know, despite the many studies reporting on the lymphatic drainage pathways from the breast and advances in breast sentinel lymphatic mapping, particularly the superficial lymphatic drainage. Gray [18] precisely dissected the dermal and subcutaneous breast lymphatics and demonstrated a rich anastomosis between breast skin and the subcutaneous and parenchymal lymphatic trunks draining toward the axilla. Several reports have proposed that the dermal lymphatic pathway defines the clinically relevant breast cancer metastatic pathway and suggest that lymphatic supply is less abundant or available in the breast parenchyma than that in the superficial dermal and subdermal layers [19,20] In the study, we found that DS < 0.765cm is more likely to lead to ALNM. This was consistent with the previous research results of ALNM and tumor depth. Ansari et al. [21] reviewed 233 cases of T1 and T2 breast cancer, and found that the distance between tumor and skin was significantly correlated with axillary lymph node positivity in multivariate analysis. For every 1 mm decrease in the distance between the tumor and the skin, the likelihood of a positive axillary lymph node increased by 15%.

The risk of breast conserving surgery for tumors in the central region of the breast is high, mainly due to the poor prognosis and more invasive clinicopathological features of tumors in the central and nipple parts compared with the surrounding quadrant [22]. The study also showed that tumors closer to the nipple more easily lead to ALNM. It is worth noting that for tumors located in the outer upper quadrant, the distance between the nipple and sentinel lymph nodes was related to ALNM. Therefore, using the nomogram of the study to find the best cut-off point can perfectly solve the contradiction between them.

We established a novel nomogram to predict ALNM, and the AUC was 0.88, indicating its satisfactory predictive effect. Additionally, the C-index of nomogram made by Song and Chen were 0.731 and 0.862 respectively. Compared with these models, our predictive nomogram achieved comparative prognostic accuracy and was more economical and convenient. The nomogram incorporates more factors than before and shows better prediction performance. What was novel was that this study used 3D model for the first time

to predict the effect of tumor location on ALNM. The results are generally consistent with previous studies, and could even better visualize the results, which is a breakthrough of this study.

It was worth noting that in this study, age, T stage, pathological type, palpable, and number of foci were not independent risk factors for ALNM, which was inconsistent with some research results. Therefore, it must be admitted that the study is a single-center retrospective study, and the number of patients is relatively small. The identified independent risk factors and prediction models need to be further verified.

In conclusion, based on nuclear grade, tumor location, LVI, DS, DN and DSLN, a novel nomogram model was established to predict the incidence of ALNM in patients with breast cancer. This model has potential value in predicting the ALNM risk. It may help oncologists make clinical decisions.

Author contribution

Luhao Sun, Zhiyong Yu contributed to conception and design of the study. Chao Li organized the database. Xinzhao Wang performed the statistical analysis. Haiyin Sun wrote the first draft of the manuscript. Sumei Li and Xiaoyu Liu wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Ethical approval statement

Studies on human participants were reviewed and approved by Shandong Cancer Hospital and Institute.

Data availability statement

Data available on request from the authors

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, et al. (2007) Cancer statistics. CA Cancer J Clin (2007) 57: 43-66. doi: 10.3322/canjclin.57.1.43.

2. Weigelt B, Peterse JL, van't Veer LJ (2005) Breast cancer metastasis: markers and models. Nat Rev Cancer 5: 591e602. doi: 10.1038/nrc1670

3. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, et al. (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 305: 569-75. doi: 10.1001/jama.2011.90

4. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, et al. (2014) 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 15: 1303–10. doi: 10.1016/S1470-2045(14)70460-7

5. Viale G, Zurrida S, Maiorano E, Mazzarol G, Pruneri G, et al. (2005) Predicting the status of axillary sentinel lymph nodes in 4351 patients with invasive breast carcinoma treated in a single institution. Cancer 2005;103(3):492e500. doi: 10.1002/cncr.20809.

6. Chua B, Ung O, Taylor R, Boyages J (2001) Frequency and predictors of axillary lymph node metastases in invasive breast cancer. ANZ J Surg 71: 723e8. doi:10.1046/j.1445-1433.2001.02266.x.

7. Eom YH, Kim EJ, Chae BJ, Song BJ, Jung SS (2015) The distance between breast cancer and the skin is associated with axillary nodal metastasis. J Surg Oncol 111: 824-8. doi: 10.1002/jso.23898.

8. Yoshihara E, Smeets A, Laenen A, Reynders A, Soens J, Van Ongeval C, et al. (2013) Predictors of axillary lymph node metastases in early breast cancer and their applicability in clinical practice. Breast. 2013 Jun;22(3):357-61. doi: 10.1016/j.breast.2012.09.003.

9. Barth A, Craig PH, Silverstein MJ (1997) Predictors of axillary lymph node metastases in patients with T1 breast carcinoma. Cancer 79: 1918e22.

10. Chadha M, Chabon AB, Friedmann P, Vikram B (1994) Predictors of axillary lymph node metastases in patients with T1 breast cancer. A multivariate analysis. Cancer 73(2):350-3.doi:10.1002/1097-0142(19940115)73:2<350::aid-cncr2820730219>3.0.co;2-5.

11. Harden SP, Neal AJ, Al-Nasiri N, Ashley S, Querci della Rovere G (2001) Predicting axillary lymph node metastases in patients with T1 infifiltrating ductal carcinoma of the breast. The Breast 2001;10:155e9. doi: 10.1054/brst.2000.0220

12. Woo CS, Silberman H, Nakamura SK, Ye W, Sposto R, Colburn W, et al. (2002) Lymph node status combined with lymphovascular invasion creates a more powerful too for predicting outcome in patients with invasive breast cancer. Am J Surg 2018: 337e40. doi:10.1016/s0002-9610(02)00950-9.

13. Okcu O, Öztürk SD, Öztürk Ç, Şen B, Yasin Aİ, et al. (2022) Tumor-infiltrating lymphocytes (TILs)/volume and prognosis: The value of TILs for survival in HER2 and TN breast cancer patients treated with chemotherapy. Ann Diagn Pathol. 58: 151930. doi: 10.1016/j.anndiagpath.2022.151930.

14. Sohn VY, Arthurs ZM, Sebesta JA, Brown TA (2008) Primary tumor location impacts breast cancer survival. Am J Surg.195: 641-4. doi:10.1016/j.amjsurg.2007.12.039.

15. Hwang KT, Kim J, Kim EK, et al. (2017) Poor Prognosis of Lower Inner Quadrant in Lymph Node-negative Breast Cancer Patients Who Received No Chemotherapy: A Study Based on Nationwide Korean Breast Cancer Registry Database. Clin Breast Cancer. 169-84. doi:10.1016/j.clbc.2016.12.011.

16. Chen YW, Lai YC, Hsu CC, Chuang YW, Hou MF (2005) Value of nodal drainage patterns and tumor location from lymphoscintigraphic mapping in detecting axillary sentinel lymph node status in breast cancer: experience at Kaohsiung Medical University Hospital. Kaohsiung J Med Sci. 251-7. doi: 10.1016/S1607-551X(09)70197-4.

17. Colleoni M, Zahrieh D, Gelber RD, et al. (2005) (28) Site of primary tumor has a prognostic role in operable breast cancer: The International Breast Cancer Study Group experience. J Clin Oncol. 23: 1390-400. doi:10.1200/JCO.2005.06.052.

18. Gray JH (1937) The lymphatics of the stomach. J Anat 492- 496:491.

19. Cunningham JE, Jurj AL, Oman L, et al. (2006) Is risk of axillary lymph node metastasis associated with proximity of breast cancer to the skin? Breast Cancer Res Treat 100:319-28. doi:10.1007/s10549-006-9256-2.

20. Chao C, Edwards MJ, Abell T, et al. (2003) Palpable breast carcinomas: A hypothesis for clinically relevant lymphatic drainage in sentinel lymph node biopsy. Breast J 9:26-32. doi:10.1046/j.1524-4741.2003.09107.x.

21. Ansari B, Morton MJ, Adamczyk DL, et al. (2011) Distance of breast cancer from the skin and nipple impacts axillary nodal metastases. Ann Surg Oncol 18: 3174-80. doi:10.1245/s10434-011-1957-z.

22. Ji F, Xiao W, Yang C, Yang M, Zhang L, Gao H, et al. (2019) Tumor Location of the Central and Nipple Portion Is Associated With Impaired Survival for Women With Breast Cancer. Cancer Manage Res 11:2915–25. doi: 10.2147/CMAR.S186205