Prediction of axillary lymph node metastases in breast cancer patients based on pathologic information of the primary tumor

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Data Collection B
Statistical Analysis C
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Background: Axillary lymph nodes (ALN) are the most commonly involved site of disease in breast cancer that has spread outside the primary lesion. Although sentinel node biopsy is a reliable way to manage ALN, there are still no good methods of predicting ALN status before surgery. Since morbidity in breast cancer surgery is predominantly related to ALN dissection, predictive models for lymph node involvement may provide a way to alert the surgeon in subgroups of patients.

Material/Methods: A total of 1325 invasive breast cancer patients were analyzed using tumor biological parameters that included age, tumor size, grade, estrogen receptor, progesterone receptor, lymphovascular invasion, and HER2, to test their ability to predict ALN involvement. A support vector machine (SVM) was used as a classification model. The SVM is a machine-learning system developed using statistical learning theories to classify data points into 2 classes. Notably, SVM models have been applied in bioinformatics.

Results: The SVM model correctly predicted ALN metastases in 74.7% of patients using tumor biological parameters. The predictive ability of luminal A, luminal B, triple negative, and HER2 subtypes using subgroup analysis showed no difference, and this predictive performance was inferior, with only 60% accuracy.

Conclusions: With an SVM model based on clinical pathologic parameters obtained in the primary tumor, it is possible to predict ALN status in order to alert the surgeon about breast cancer counseling and in decision-making for ALN management.

MeSH Keywords: **Metastasis, Lymphatic • Breast Carcinoma • Support Vector Machine • Lymph Node • Sentinel Lymph Node Biopsy**

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Background

Axillary lymph nodes (ALN) are the most commonly involved site of disease in breast cancer that has spread outside the primary lesion. ALN status plays an important prognostic role in female invasive breast cancer [1–4]. For tumor staging and treatment, complete ALN dissection (ALND) was a standard surgical approach in the early 20th century. However, ALND was accompanied with some troublesome clinical problems; morbidities including lymphedema, paresthesias, and major nerve and vessel injury are well-documented [5–7]. These problems led physicians to seek alternative approaches in the assessment of ALN status.

The sentinel lymph node is the primary site of ALN metastasis (ALNM) from breast cancer. The concept of the sentinel lymph node was applied in penile carcinoma in the 1970's [8], and was soon applied to breast cancer. Patients gained benefit from sentinel lymph node biopsy (SLNB) in terms of surgical morbidities and accurate tumor staging [9]. Today, SLNB is a reliable and standard method in the assessment of axillary status in early invasive breast cancer [10]. However, there are still no good methods to predict ALN status before surgery. Since morbidity in breast cancer surgery is predominantly related to ALND, predictive models for lymph node involvement may provide a way to alert the surgeon in subgroups of patients. The primary aim of this study was to determinate the predictive factors of ALN metastasis using pathologic information.

Material and Methods

Patient population, data collection, and definition of cases

This was a retrospective study of female patients with invasive breast cancer at Changhua Christian Hospital between January 2004 and January 2010. The clinical data and tumor characteristics for all invasive breast cancers had been collected in our breast cancer database. This study was approved by the institutional review board and ethics committee of Changhua Christian Hospital. Breast cancer patients who had undergone surgery were identified. The exclusion criteria were: 1) ductal carcinoma *in situ*; 2) neoadjuvant therapy; 3) bilateral invasive breast cancer; and 4) patients without breast-conserving surgery with ALND or sentinel lymph node sampling or modified radical mastectomy.

The clinical characteristics assessed were age at diagnosis, tumor size, positive lymph node, histology grade, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, and the presence of lymphovascular invasion (LVI). All information was retrospectively analyzed so as to identify patients who might have had a risk of ALN metastasis pre-operatively.

Statistical analysis

The support vector machine (SVM) is a statistical learning theory developed to classify data points into 2 classes [11,12]. SVMs are powerful statistical methods in classification. This study utilized the SVM system to classify the axillary status of breast cancer. The pathologic features of a primary breast tumor were formed into a multi-dimensional feature vector, and then used as the input signals for the SVM classifier. When the output value of a patient was greater than or equal to zero, the CAD system would diagnose the patient as having positive ALNM. Conversely, when the output value was smaller than zero, the case would be classified as negative ALNM. The performance measure, which was the receiver operating characteristic curve (ROC) analysis, was used to estimate the performance of the proposed system. The Az value (area under the ROC) was used to evaluate the significance of each clinical feature.

Results

A total of 1325 patients with a mean age of 51 years (SD=11.2) were included in this study. Of these, 742 patients had positive ALNM. The mean tumor size was 24.4 mm (SD=1.5); 39% of the patients had T1 tumors (20 mm), followed by 54% with T2 tumors and 7% with T3 tumors. The histology grade was predominantly grade II (55%), with 28% grade III and 17% grade I tumors. Lymphovascular invasion was found in 573 patients (43%). The ER/PR/HER2 profile showed 847 patients (63.9%) had luminal A type tumors, followed by 16.1% with triple-negative tumors, 13.1% with luminal B type tumors, and 6.9% with HER2-positive tumors. Relevant details of this study population are listed in Table 1.

Table 2 presents the observed results of SVM classification. Discordant results were noted between SVM and pathology reports in 341 cases; 141 out of 583 patients were positive for ALNM but were classified as negative, and 200 out of 742 negative ALNM patients were classified as positive for ALNM by SVM. The sensitivity and specificity were 76% and 73%, respectively. The positive predictive value was 69% and negative predictive value was 79%. The accuracy rate was 74% (Table 3).

ROC curves were used to analyze the diagnostic performance of the SVM by clinical pathology features. The cutoff value to balance sensitivity and specificity was 0.000325182. If the output of SVM was smaller than 0.000325182, then it was defined as negative for ALNM, and values greater than or equal to 0.000325182 were classified as positive axillary nodal status. A higher Az value indicated a better diagnostic performance. The Az value of this study was 0.7682 by SVM (Figure 1).

Table 1. Characteristics and tumor features of breast cancer patients.

Variables	Axillary lymph node metastases					
	Negative (N=742)		Positive (N=583)		Total (N=1,325)	
Age, mean (SD)	51.12	(11.06)	51.43	(11.38)	51.25	(11.20)
Clinical factors						
Tumor size, mean (SD)	2.08	(1.164)	2.91	(1.659)	24.44	(1.461)
<2 cm	356	(47.98)	159	(27.27)	515	(38.87)
2–5 cm	356	(47.98)	360	(61.75)	716	(54.04)
≥5 cm	30	(4.04)	64	(10.98)	94	(7.09)
Grade						
1	143	(19.27)	72	(12.35)	215	(16.23)
2	415	(55.93)	320	(54.89)	735	(55.47)
3	184	(24.80)	191	(32.76)	375	(28.30)
Pathological factors						
Estrogen receptor						
Negative	256	(34.50)	177	(30.36)	433	(32.68)
Positive	486	(65.50)	406	(69.64)	892	(67.32)
Progesterone receptor						
Negative	291	(39.22)	183	(31.39)	474	(35.77)
Positive	451	(60.78)	400	(68.61)	851	(64.23)
HER2						
Negative	616	(83.02)	444	(76.16)	1,060	(80.00)
Positive	126	(16.98)	139	(23.84)	265	(20.00)
ER/PR/Her2 profile						
Triple negative						
No	598	(80.59)	514	(88.16)	1112	
Yes	144	(19.41)	69	(11.84)	213	
HER2-positive						
No	692		542		1234	
Yes	50		41		91	
Luminal A						
No	270		208		478	
Yes	472		375		847	
Luminal B						
No	666		485		1151	
Yes	76		98		174	
Lymphovascular invasion (LVI)						
No	585	(78.84)	167	(28.64)	752	(56.75)
Yes	157	(21.16)	416	(71.36)	573	(43.25)

Table 2. Observed results in this study.

| | | Axillary lymph node metastases | | |
		Positive	Negative	Total
SVM	Positive	442	200	642
	Negative	141	542	683
	Total	583	742	1325

Table 3. SVM results.

	%	95% CI	
Sensitivity	75.81	0.72338798	0.792907046
Specificity	73.05	0.698530725	0.762385717
Positive predictive value	68.85	0.65264906	0.724297981
Negative predictive value	79.36	0.763202555	0.823913111
Accuracy	74.26	0.71910148	0.766181538

Discussion

Complete ALND is an important procedure in cancer staging and local control of disease. However, ALND has some unfavorable complications, including numbness, lymphedema, and major vessel and nerve injury [13–15]. Nowadays, SLNB plays an important role in evaluating axillary nodal status. The greatest benefits of SLNB are its effectiveness and low number of operative complications. Patients with a small tumor might benefit from SLNB. In fact, SLNB is routinely performed in clinically axillary nodal-negative patients.

Primary pathologic characteristics and clinical features are useful in the assessment of axillary nodal involvement [14–16]. Our objective was to clarify the relationship between pathologic characteristics and ALNM. Based on our previous research [17–19], the SVM has been found to be a useful diagnostic tool in dealing with binominal data. In this study, we constructed a powerful statistical method with pathologic features, including tumor size, LVI and histology grade, and ER, PR, and HER2 status. The output of SVM in our study was analyzed using the ROC curve, and the diagnostic performance (Az value=0.7682) was acceptable.

There remains much debate about the relationship between pathologic characteristics and ALNM. Barth et al. found that tumor size, LVI, and histology grade were important factors in predicting ALNM [20]. The definition of LVI is the presence of an invasion of cancer cells into the blood vessels or lymphatic channels. Positive LVI is correlated with aggressive tumor
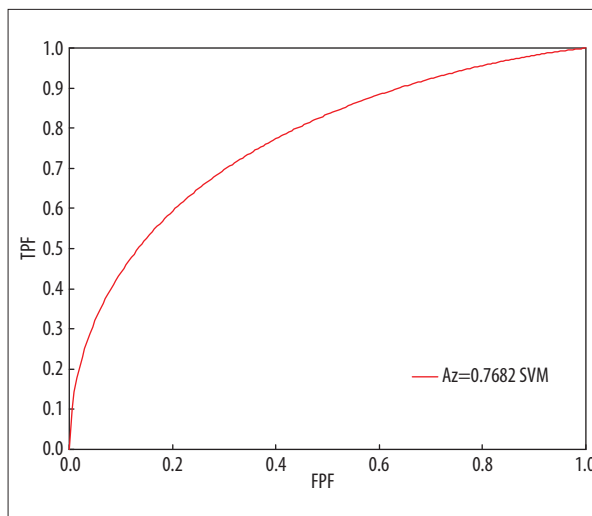

Figure 1. Diagnostic performance of SVM using the ROC curve.

behavior and metastatic ability [21]. LVI has been consistently shown to be predictive of ALNM in many studies [20–29]. The odds ratio (LVI presence *vs.* negative) is high in extensive axillary nodal involvement. In small invasive breast cancer with negative LVI, the incidence of ALNM is low [22]. The LVI also increases the incidence of non-sentinel lymph node metastases and isolated tumor cells in the sentinel lymph node [29,30]. The presence of LVI as the most important predictor is well accepted. Our study also confirms LVI is the strongest single predictor in ALNM.

Histology grade and tumor size are also important predictors of ALNM. The probability of ALNM is high if a patient has a large tumor and high histology grade. Our data presented in Table 1 reveal that patients with a large tumor (more than 5 centimeters in size) and a high histology grade are more likely to have ALNM, a finding that is consistent with those of previous studies [20,31–33]. Patients with small invasive breast cancer might benefit from SLNB [34]. Our study showed that patients with a tumor less than 2 centimeters in size and a low-to-medium histology grade are good candidates for SLNB.

Regional lymph node status is necessary for tumor staging and surgical planning. Previous studies have found some important factors in predicting ALNM, but the predictive power was not acceptable. With the advances in surgical technique, SLNB is now widely used in early breast cancer and is becoming a standard procedure in clinical ALN-negative patients. The benefits of SLNB are fewer surgical complications than complete ALND and the efficacy and accuracy after long-term follow-up [35]. The importance of SLNB is clear. In this study, the clinical pathologic characteristics were found to be useful in predicting cancer prognosis. We thus offer an auxiliary method in the assessment of axillary status pre-operatively, but not to replace SLNB.

Conclusions

With a model based only on clinical routine pathologic parameters obtained from the primary tumor, it is possible to predict ALN status. This may help the surgeon in breast cancer counseling and decision-making for ALN management.

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