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Original Article

Analysis of risk factors for axillary metastasis in sentinel lymph node positive breast cancer patients

Li Huang[1,2], Jun Zhang[1], Zhicheng Ge[1], Xiang Qu[1]

[1]*Department of General Surgery, Beijing Friendship Hospital, Capital Medical University, Beijing City, China;* [2]*Department of Breast Surgery Ward No.3, The Affiliated Tumor Hospital of Shanxi Medical University, Shanxi Tumor Hospital, Taiyuan, Shanxi Province, China*

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Abstract: Objective: To investigate the risk factors for axillary metastasis in patients with sentinel lymph nodes (SLN) positive breast cancer (BC). Methods: Pathological data of 192 BC patients with positive results of sentinel lymph node biopsy who underwent axillary lymph node dissection (ALND) were analyzed. The predictive model of the Memorial Sloan-Kettering Cancer Center (MSKCC) was used to predict the risk of axillary non-SLN metastasis in patients, and the accuracy of the model was evaluated by the receiver operating characteristic (ROC) curves. Results: The results showed no statistical differences in age, tumor type, estrogen receptor expression, tissue differentiation, and the number of negative SLNs (all $P > 0.05$), but statistical differences in tumor size, tumor number, the number of positive SLNs, and SLN metastasis rates were significant (all $P < 0.05$). Multivariate logistic analysis showed that the tumor size, the number of tumors, and positive SLN rates were independent risk factors for non-SLN metastasis. The area under the ROC curve of the MSKCC model was 0.771. Conclusion: Tumor size, the number of tumors, and positive SLN rates are independent risk factors for axillary non-SLN metastasis in SLN-positive patients. If the SLN is positive associated with the presence of these clinical symptoms, ALND is therefore advised. The MSKCC model has a high predictive accuracy for breast cancer patients with non-SLN metastasis.

Keywords: Breast cancer, sentinel lymph node, axillary metastasis, risk factors

Introduction

Breast cancer (BC) is the most common malignant tumor in women currently [1]. More than 249,000 people were diagnosed with BC in the United States in 2016, and over 40,000 people die from BC or its complications annually [2]. In recent years, the age of onset is younger with an increasing incidence year by year, which imposes a great threat to both quality of life and life expectancy of patients [3]. Due to the advances in medical technologies, early screening of BC has promoted; therapies for BC are improving constantly. Studies now suggest that, the number of BC patients is increasing on a yearly basis, so does the 5-year survival rate [4].

Axillary lymph node dissection (ALND) is the standard treatment regimen for metastatic tumors of BC patients [5]. Axillary lymph node (ALN) is an important indicator that is used to assess both BC prognosis and treatment. Study has shown that it is an indicator to identify the stage of BC disease and involvement of ALN, and tumor-related deaths in BC patients significantly increase when ALN is involved [6]. At present, sentinel lymph node biopsy (SLNB) is performed to detect ALN metastasis. When SLNB is negative, patients do not require ALND. When the SLNB is positive, ALND is required [7]. However, in T1-T2 stage BC patients, even when patients are SLN positive, more than 50% have no metastasis of non-SLN; however, excessive ALND treatment was performed in many of those patients [8]. There are many factors for non-SLN metastasis in SLN-positive BC patients. Most hospitals have established a non-SLN model to identify this type of BC in clinical practice. The Memorial Sloan-Kettering Cancer Center (MSKCC) is the first center that can predict non-SLN in SLN-positive BC patients, and the model has been verified in numerous hos-

Table 1. Lymph node metastasis

Group	Axillary non-SLN metastases patients (n=108)	No axillary non-SLN axillary metastases patients (n=84)	χ^2	P
T1 (n=85)	40 (37.04)	45 (53.57)	5.425	0.066
T2 (n=100)	63 (58.33)	37 (44.05)		
T3 (n=7)	5 (4.63)	2 (2.38)		

Note: SLN, sentinel lymph node.

pitals and medical centers [9]. Study has also reported that the accuracy of non-SLN predictions can be improved using the MSKCC model [10].

In this study, we retrospectively analyzed the pathological data of patients in the Thyroid and Breast Surgery Clinic who underwent SLNB to verify the MSKCC model for its predictive capabilities.

Materials and methods

Patients

The study was approved by the Medical Ethics Committee of the Beijing Friendship Hospital, and all patients signed written informed consent.

The pathological data of 192 BC patients with positive SLNB who underwent ALND in Beijing Friendship Hospital from January 2013 to December 2016 were analyzed. In this study cohort, all patients were female. The age of the patients was 35-71 years, with an average age of 50.4±12.8 years. The seventh edition of the American Joint Committee on Cancer was applied to perform tumor, node and metastasis staging in BC patients [11]. Specific clinical data of the patients was collected.

Inclusion criteria: a) Patient older than 18 years old; b) Diagnosed with BC by cancer pathologic biopsy prior to surgery, with a tumor size < 50 mm; c) No chemotherapy or radiotherapy prior to surgery; d) At least 1-2 SLN metastases confirmed by ALND; e) Suspicious ALN positive indicated by ultrasound.

Exclusion criteria: Patients with congenital diseases, family genetic history, defective limbs and immunodeficiency associated disease; with incomplete clinical data; with other malignant tumors, or distal metastases confirmed by preoperative imaging examination.

Identification of SLN and case examination

In this study, all BC patients were injected with methylene blue of 2 mL around the breast mass using the 4-point method, followed by massaging for 5 minutes. An arcuate incision was made in the outer edge of the pectoralis major, which was cut layer by layer; blue-stained lymphatic vessels were identified and tracked. Blue-stained lymph node tissue was removed for frozen biopsy, HE staining and biopsy along with other tumor specimens.

Statistical analysis

All collected data were assessed for statistical analyses by using SPSS 20.0 software, and the desired images were drawn using Graphpad Prism 7.0. Enumeration data are expressed as a percentage (%) and assessed using the Chi square test. Taking the single factor $P < 0.05$ index as the independent variable, and the BC non-SLN metastasis as the dependent variable; stepwise logistic regression was used for multivariate analysis. $P < 0.05$ indicates a statistically significant difference.

Results

Lymph node metastasis

Amongst the SLN-positive patients, 108 had axillary non-SLN metastases and 84 patients had no axillary non-SLN axillary metastases. This included 85 patients of T1, 100 patients of T2, and 7 patients of T3. No differences between the two groups were observed ($P > 0.05$; **Table 1**).

Univariate analysis of axillary non-SLN metastases and clinical pathological data

Univariate analysis of patient data with/without axillary non-SLN metastases showed that no significant differences in age, tumor type, estrogen receptor expression, tissue differentiation,

Table 2. Univariate analysis of axillary non-SLN metastases and clinical pathological data of patients

Group	Axillary non-SLN metastases patients (n=108)	No axillary non-SLN axillary metastases patients (n=84)	χ^2	P
Age (year)			2.337	0.126
> 45 (n=92)	57 (52.78)	35 (41.67)		
≤ 45 (n=100)	51 (47.22)	49 (58.33)		
Tumor type			0.101	0.751
Invasive ductal carcinoma (n=150)	85 (78.71)	65 (77.38)		
Invasive lobular carcinoma (n=20)	12 (11.11)	8 (9.52)		
Invasive mixed carcinoma (n=13)	7 (6.48)	6 (7.15)		
Other types of cancer (n=9)	4 (3.70)	5 (5.95)		
Vascular infiltration				0.505*
Yes (n=2)	2 (1.85)	0 (0.00)		
No (n=190)	106 (98.15)	84 (100.00)		
Estrogen receptor			0.252	0.616
Positive (n=100)	55 (50.93)	45 (53.57)		
Feminine (n=80)	45 (41.67)	35 (41.67)		
Not checked (n=12)	8 (7.40)	4 (4.76)		
Progesterone receptor			2.896	0.089
Positive (n=95)	60 (55.56)	35 (41.67)		
Feminine (n=85)	41 (37.96)	44 (52.38)		
Not checked (n=12)	7 (6.48)	5 (5.95)		
Human epidermal growth factor-2			0.005	0.944
Positive (n=97)	55 (50.93)	43 (51.19)		
Feminine (n=83)	47 (43.52)	35 (41.67)		
Not checked (n=12)	6 (5.55)	6 (7.14)		
Organizational differentiation			0.338	0.561
Low (n=58)	37 (34.26)	21 (25.00)		
Medium (n=72)	35 (32.41)	37 (44.05)		
High (n=62)	36 (33.33)	26 (30.95)		
Tumor size			48.276	< 0.001
≥ 20 mm (n=98)	79 (73.15)	19 (22.62)		
< 20 mm (n=94)	29 (26.85)	65 (77.38)		
Number of tumors			19.231	< 0.001
Single (n=108)	46 (42.59)	62 (73.81)		
Multiple (n=84)	62 (57.41)	22 (26.19)		
Number of positive SLN			21.815	< 0.001
Single (n=133)	60 (55.56)	73 (86.90)		
Multiple (n=59)	48 (44.44)	11 (13.10)		
Number of negative SLN			47.492	0.115
Single (n=115)	70 (64.81)	45 (53.57)		
Multiple (n=77)	38 (35.19)	39 (46.43)		
SLN transfer rate			2.924	0.004
> 50% (n=129)	82 (75.93)	47 (55.95)		
≤ 50% (n=63)	26 (24.07)	37 (44.05)		

Note: SLN, sentinel lymph node. *Examined by Fisher exact text.

and the number of negative SLNss were observed between the two groups (all P > 0.05). However, significant differences in tumor size, the number of tumors, the number of positive

Table 3. Multivariate analysis of non-SLN metastases

Factor	β	SD	χ^2	OR	95% CI	P
Tumor size	0.782	0.425	5.941	0.472	0.225, 0.836	0.013
Number of tumors	0.584	0.148	8.684	0.638	0.387, 0.805	0.008
Positive SLN rate	0.841	0.465	6.251	0.428	0.201, 0.825	0.019

Note: SLN, sentinel lymph node; SD, standard deviation; OR, odds ratio; CI, confidence interval.

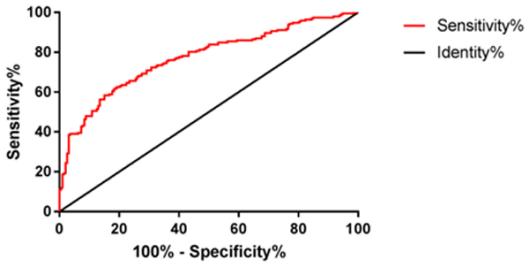

Figure 1. MSKCC predictive model verification. The analysis revealed that the AUC=0.771 and 95% CI was 0.724, 0.818. MSKCC, Memorial Sloan-Kettering Cancer Center; AUC, area under the curve; CI, confidence interval.

SLNs, and SLN metastasis rates were observed (all P < 0.05; **Table 2**).

Multivariate analysis of non-SLN metastases

Following univariate analysis, multivariate logistic analysis was performed. This analysis showed that tumor size, the number of tumors, and the positive SLN rates were independent risk factors for non-SLN metastasis (**Table 3**).

MSKCC predictive model verification

Calculation of the non-SLN metastasis rate using the MSKCC model and the receiver operating characteristic curve in the current study showed that the area under the curve (AUC)=0.771 and the 95% CI was 0.724, 0.818 (**Figure 1**).

Discussion

As a common malignant tumor in women, BC often presents as a painless breast mass, and in the advanced stages, skin depression and shape changes may occur [12]. Study has shown that a lack of exercise, obesity, and family history (amongst other factors) are all BC risk factors [13]. The 5-year survival rate of BC patients in developed countries can be up to 80% or even higher, but these numbers are lower in developing countries [14]. Surveys performed in 2012 showed that 1.68 million new cases of BC were reported globally, and more than 520,000 patients died of BC [15]. There is also a growing trend of BC towards younger people, which has a bad impact on life expectancy and future quality of life in the population. In the present day, the major treatments for BC include surgical resection, radiotherapy, chemotherapy and endocrine therapy [16, 17]. For many years, the surgery was widely employed in clinical practice. However, with advanced treatment protocols, more care is taken to preserve general health without compromising therapeutic benefits. This requires the support of more advanced medical knowledge and technology [18].

ALND is an important part of the surgical procedure for invasive BC. However, ALND can easily lead to a series of adverse reactions, including lymphedema and a loss of consciousness, which not only prolongs hospitalization time of patients with increasing economic burden of the family, but also seriously impacts quality of life of the patients [19]. SLNB is an important operative procedure for early ALN staging in BC patients. SLNB can avoid dissection in SLN negative patients; thus, it reduces the occurrence of postoperative complications [20]. ALND is required only when SLNB is positive. However, ALND is generally performed in all SLN-positive patients, but non-SLN metastasis are not present in up to 50% of cases, resulting in over-treatment [21]. Thus, when SLN is positive, early BC patients can be prevented from overtreatment by means of prediction of non-SLN metastasis.

In this study, we retrospectively analyzed 192 SLN-positive to identify the risk factors of axillary non-SLN metastasis in patients with SLN metastasis. Univariate analysis of the two groups showed that age, tumor type, estrogen receptor expression, tissue differentiation, and the number of negative SLNs were not associated with axillary non-SLN metastasis, whilst tumor size, tumor number, the number of positive SLNs, and SLN metastasis rate were associated with axillary non-SLN metastasis. In the

study by Mittendorf et al., univariate analysis also showed that tumor size, tumor number, the number of positive SLNs and SLN metastasis rates were correlated with axillary non-SLN metastasis, which was consistent with the results of this study [22].

Subsequently, multivariate logistic analysis showed that tumor size, tumor number and positive SLN rates were independent risk factors for axillary non-SLN metastasis. In the study by Viale et al., multivariate analysis also showed that tumor size, the number of tumors and SLN positive rates were independent risk factors for axillary non-SLN metastasis, again consistent with our data [23]. The MSKCC axillary non-SLN metastasis prediction model obtained an AUC of 0.76 by verifying the clinical data of 373 SLN-positive BC patients, which was in accordance with the range of 0.58-0.86 obtained by many national medical centers and hospitals [24, 25]. In this study, the AUC was 0.771, indicating that the model could well predict the non-SLN metastasis.

There are however, some limitations of this study. The small sample size impacted the accuracy of the data and we did not perform follow-ups after surgery. Thus, whether BC recurrence occurred in the post-surgery patient was not clear. In future studies, we hope to increase the sample size and verify all findings with long-term follow-ups.

In conclusion, this study confirmed that tumor size, the number of tumors and SLN positive rates were independent risk factors for axillary non-SLN metastasis in SLN-positive patients. When patients were positive for SLN and presented these clinical symptoms, they were recommended to undergo ALND. The MSKCC model displayed a high accuracy for predicting non-SLN BC in patients.

Disclosure of conflict of interest

None.

Address correspondence to: Jun Zhang, Department of General Surgery, Beijing Friendship Hospital, Capital Medical University, No.95 Yong'an Road, Xicheng District, Beijing City 100050, China. Tel: +86-13811055986; Fax: +86-010-63138754; E-mail: zhangjun5ac@163.com

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