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ORIGINAL RESEARCH

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The value of ultrasonic parameters combined with clinicopathological parameters in predicting axillary lymph node metastasis in triple-negative breast cancer

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Abstract

The clinical data of 119 patients with triple-negative breast cancer (TNBC) were retrospectively analyzed, and comparisons revealed that the differences between those who developed axillary lymph node metastasis and those who did not were statistically significant when comparing the age, histological grading of the lesions, expression of Ki-67, and information about the morphology of the lesions, internal blood flow, and the ultrasonographic manifestations of axillary lymph nodes on ultrasonography of the distribution of the lesions in the lesions' quadrants ($p < 0.05$). Multifactorial regression analysis suggested that age, histological grade, lesion quadrant, and axillary lymph node ultrasound performance were all relevant factors affecting axillary lymph node metastasis in TNBC patients; the predictive model of axillary lymph node metastasis in TNBC was constructed with the results of multifactorial regression analysis, and the results of the ROC curve analysis showed that the logistic regression model had an AUC of 0.761 and the sensitivity and specificity were 0.824 and 0.714, respectively, for predicting the metastasis of the axillary lymph nodes in TNBC patients. This suggests that ultrasound combined with pathological parameters has some value in helping clinical judgment of axillary lymph node metastasis in TNBC patients.

Keywords

Triple-negative breast cancer; Ultrasound; Pathological parameters; Predictive value

1. Introduction

Triple-negative breast cancer (TNBC) is 15–20% compared to the other kinds of breast cancer. It initiates at earlier age with higher tumor staging and poor prognosis [1–3]. Surgeons perform prophylactic axillary lymph node dissection to improve the prognosis of breast cancer patients. However, the data indicate that many patients do not have preoperative axillary lymph node metastasis, and its blind dissection may increase the postoperative complications and thus reduce the patients' life quality [4, 5]. Sentinel Lymph Node Biopsy (SLNB) has gradually supplanted the axillary lymph node dissections because of advancements in breast surgery procedures. Sentinel Lymph Node (SLN) is an initial axillary metastatic location for breast cancer. Metastasis to the next location of lymph node is less likely if SLN metastasis does not occur, however the definition of SLNB indication is lacking [6–8]. The prediction of axillary lymph node metastasis is significant for minimizing the unnecessary axillary lymph node dissection and enhancing the patients' prognosis [9].

2. Objects and methods

2.1 Research subjects

A retrospective analysis was conducted according to the standards of ethical committee of our hospital. The study included 119 TNBC patients admitted to Xuzhou City Hospital of Traditional Chinese Medicine, Xuzhou Cancer Hospital, and Affiliated Hospital of Xuzhou Medical University between June 2021 and June 2022.

(1) Inclusion criteria: female patients; availability of axillary lymph node biopsy pathological report; postoperative pathological examination to confirm TNBC diagnosis; unilateral lesions with breast ultrasound examination before surgery; and availability of complete and clear imaging data.

(2) Exclusion criteria: received local radiation therapy, endocrine therapy or systemic chemotherapy before the breast ultrasound examination; and missing medical records.

2.2 Methods

2.2.1 Lymph node biopsy and surgical approach

Clinically suspicious axillary lymph nodes patients underwent preoperative fine-needle aspiration or core biopsy. The axillary lymph nodes of patients with positive biopsy results and

undergoing direct surgery (rather than neoadjuvant therapy) were cleared during the breast surgery. Patients of negative biopsy results did not require more testing before the surgery. Complete axillary node clearance was not required for patients with one or two pathologically involved sentinel nodes, however, it was performed for three or more.

2.2.2 Ultrasound breast examination and the parameters collection

The preoperative ultrasound mammography was conducted for all the patients. GE-E10 and L12-5-line array probes with optional breast mode were employed as the examination instruments. The senior and experienced ultrasonographers performed the clinical examinations. Patients were examined in the lying position with hands raised or under the head to expose breast and armpit. An ultrasonic scan was made by the clock method with nipple at the center. As the mass was found, ultrasound parameters such as location, diameter, morphology, margins, internal echogenicity, internal blood flow, calcification, and posterior echogenic changes, and distance from the nipple were recorded as per the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) [10]. The bilateral axillae located ipsilateral to breast lesion in the scan and having following characteristics were considered positive for the lymph node ultrasound:

spherical lymph nodes; aspect ratio (L/S) $<$2.0; eccentric cortical thickening with maximum thickness $\geq$3.0 mm; disappearance of lymphatic node; and thinning or disappearance of medulla.

2.2.3 Clinical pathology parameter collection

Immunohistochemical test results including Estrogen receptor (ER), Progesterone receptor (PR), Human epidermal-growth-factor receptor 2 (HER-2), Ki-67 and p53 could be categorized as the TNBC patients. p53 was graded as per the number of positive cells with $\geq$10% defined as positive, Ki-67 of $\leq$20% as low proliferation, and $>$20% as high proliferation. Clinical data pertaining to the patient's age, menopausal status, body mass index, reproductive history, family history of breast cancer, and histological grading were collected.

2.3 Statistical methods

Relevant data were entered into statistical software SPSS (19.0, IBM, Armonk, NY, USA) for the analysis. The count data were expressed as percentages in χ^2 test, and measurement data as ($\bar{x} \pm s$) in the t-test. Statistically significant variables in single-factor analysis were subjected to multi-factor logistic regression analysis. The variables were screened using backward method. $p < 0.05$ was considered statistically significant.

3. Results

3.1 Analysis of relationship between axillary lymph node metastasis and clinicopathological data

Postoperative pathology confirmed the axillary lymph node metastasis in 36 cases, while its absence in 83 cases. Analysis in Table 1 revealed that the differences in age, histological grading of lesions, and Ki-67 expression between those of with and without lymph node metastasis were statistically significant ($p < 0.05$).

3.2 Relationship between axillary lymph node metastasis and ultrasound imaging parameters

The differences between those of with and without axillary lymph node metastasis were statistically significant ($p < 0.05$) regarding quadrant distribution, morphology, internal blood flow and ultrasound presentation (Table 2).

3.3 Multi-factor regression analysis of axillary lymph node metastasis in TNBC patients

Multi-factor regression analysis depicted that the age, histological grading, quadrant at lesion location, and ultrasound performance were the relevant factors affecting axillary lymph node metastasis in TNBC patients (Table 3).

4. Discussion

Breast tumor is malignant with the highest global incidence rate in females and posing threats to the health and lives of patients [11–13]. The breast cancer prevalence in Chinese women has increased in recent years because of the societal development and changes in women's social roles [14–16]. The medical technologies are vigorously being developed wherein the clinical focus is placed on individualized and precise treatment design with accurate assessment of the patients [17–21]. The developing SLNB technique has prevented unnecessary axillary lymph node dissections and reduced surgical complications. However, there are patients with upper limb edema after SLNB, and reveal false-negative results [22, 23].

TNBC is a diverse breast cancer with negative ER, PR and HER-2 expression in the lesion. TNBC is a more clinically fretting kind of breast cancer compared to other forms because of its earlier initiation, aggressiveness and higher likelihood of postoperative recurrence [24, 25]. In this study, it was found that clinicopathological data such as age, histological grading of lesion, and Ki-67 expression were statistically significant when compared for TNBC patients with and without axillary lymph node metastasis. Moreover, there were differences in the quadrant distribution of lesion location, morphology, internal blood flow, and ultrasonographic manifestation of axillary lymph nodes between the two. Logistic regression model analysis revealed that age, histologic grading, lesion quadrant, and axillary lymph node ultrasound performance were the relevant factors affecting axillary lymph node metastasis in TNBC patients.

It was also revealed that female TNBC patients of lower age were more likely to have axillary lymph node metastasis [26, 27]. This work found that the risk of axillary lymph node metastasis in TNBC patients aged $>$45 years was 0.45 times higher than in $\leq$45 years. It suggested close relationship between age and axillary lymph node metastasis in TNBC patients. Higher histological grading also proposed higher malignancy, poorer tumor differentiation and greater

TABLE 1. Analysis of the relationship between axillary lymph node metastasis and clinicopathological data.

Clinicopathological data	Subgroups	Metastatic (n = 36)	Non-metastatic (n = 83)	χ^2	p
Age					
	≤45 age	18	17	10.538	0.001
	>45 age	18	66		
Menopause					
	Yes	24	50	0.441	0.507
	No	12	33		
BMI					
	<18.5 kg/m^2	4	10		
	18.5~25 kg/m^2	25	60	0.261	0.878
	>25 kg/m^2	7	13		
Fertility status					
	Yes	35	78	0.553	0.457
	No	1	5		
Family history of breast cancer					
	Yes	2	4	0.028	0.866
	No	34	79		
Histological grading					
	I~II Grade	18	66	10.538	0.001
	III~IV Grade	18	17		
Tumor site					
	Left breast	20	50	0.228	0.633
	Right breast	16	33		
p53					
	Positive	15	43	1.034	0.309
	Negative	21	40		
Ki-67					
	Positive	25	35	7.473	0.006
	Negative	11	48		

BMI: Body mass index.

invasiveness [28]. The breast ultrasonography findings with pathological parameters could suggest the axillary lymph node metastasis. In this study, it was found that higher proportion of TNBC patients with axillary lymph node metastases were in the outer upper quadrant of breast. A multifactorial regression analysis revealed that the TNBC patients with lesions located in outer upper quadrant were more likely to develop axillary lymph node metastases. According to other studies, there were differences in the locations of tumor lymphatic drainage sites in breast's quadrants. Lymph in the medial quadrant of breast drained more into the internal breast lymph nodes while the lymph in outer upper quadrant drained more into axillary lymph nodes [29]. Spherical lymph nodes, L/S 2.0, eccentric cortical thickening with maximum thickness of 3.0 mm, lymph nodes disappearance and thinning or absence of medulla in axillary ultrasonography were the indicators of positive axillary lymph nodes. The ultrasonography displayed lymph node disappearance sign when tumor cells infiltrated the lymph node. This was a symptom that lymphatics and their marginal sinuses had been invaded by the cancer cells [30]. Herein, it was found that positive axillary lymph node ultrasound performance was a relevant factor for lymph node metastasis, however, it might also be caused by the presence of immune response hyperplasia. So, there was a certain number of false positive results.

5. Conclusions

In summary, age, histological grading, quadrant of lesion, and axillary lymph node ultrasound performance were the relevant factors affecting axillary lymph node metastasis in TNBC patients. The strength of this study was laid in providing a reference for preoperative judgment of axillary lymph node metastasis in TNBC which could improve effectiveness of preoperative assessment of patients' conditions. However, the sample size included in this work was small and based

TABLE 2. Relationship between axillary lymph node metastasis and ultrasound imaging parameters.

Ultrasound imaging parameters	Subgroups	Metastatic (n = 36)	Non-metastatic (n = 83)	χ^2	p
Quadrant					
	Upper outer	27	38	10.491	0.015
	Outside down	2	10		
	Inside up	3	18		
	Inside down	4	17		
Diameter					
	<2.0 cm	7	34	4.845	0.089
	2.0~5.0 cm	24	43		
	>5.0 cm	5	6		
Shape					
	Irregular	35	65	6.691	0.010
	Regular	1	18		
Edge					
	Even	8	23	0.393	0.531
	Uneven	28	60		
Internal echo					
	Uniform	5	8	0.466	0.495
	Uneven	31	75		
Internal blood flow					
	0~I Grade	14	15	5.904	0.015
	II~III Grade	22	68		
Calcification of lesions					
	Yes	11	22	0.206	0.650
	No	25	61		
Posterior echogenic changes					
	No change	29	63	0.793	0.851
	Decay	3	9		
	Enhancement	3	6		
	Mixing	1	5		
Distance from nipple					
	Central zone	20	48	0.053	0.818
	Surrounding area	16	35		
Axillary lymph node ultrasound performance					
	Positive	26	33	10.585	0.001
	Negative	10	50		

TABLE 3. Multi-factor regression analysis affecting axillary lymph node metastasis in TNBC patients.

Factors	β	SE	Wald χ^2 value	OR	p	95% CI
Age	−0.798	0.325	6.029	0.450	0.014	0.238~0.851
Histological grading	0.844	0.278	9.217	2.326	0.003	1.349~4.010
Ki-67	0.465	0.255	3.325	1.592	0.069	0.966~2.624
Lesion quadrant	0.461	0.137	11.323	1.586	<0.001	1.212~2.074
Morphology	0.645	0.388	2.763	1.906	0.100	0.891~4.077
Internal blood flow	1.214	0.798	2.367	3.367	0.125	0.717~15.807
Axillary lymph node ultrasound performance	1.458	0.515	8.015	4.297	0.005	1.566~11.792

SE: Regression coefficient; OR: Odds Ratio; CI: Confidence Interval.

on single-center study. The conclusions obtained might have some bias.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

JZ and HYP—designed the study and carried them out; JZ, HYP, SKZ, QZ and TZ—supervised the data collection, analyzed the data, interpreted the data, prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Xuzhou City Hospital of Traditional Chinese Medicine (Approval no. 2017-006). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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