RESEARCH COMMUNICATION

Factors Influencing Axillary Lymph Node Metastasis in Invasive Breast Cancer

Ling Li[1], Li-Zhang Chen[2]*

Abstract

Purpose: To explore the relationship between auxiliary lymph node metastasis and clinical features, and to identify the factors that affect metastasis occurrence. Methods: A total of 164 cases of primary breast cancer were selected to investigate features such as age, concomitant chronic disease and pathologic diagnosis. Immunohistochemistry was used to detect the expression of the estrogen receptor (ER) and CerbB-2. Logistic regression was employed to analyze the factors that affect the incidence of lymph node metastases. Results: The incidence of lymph node metastases was 46.3% among elderly patients with breast cancer. Based on logistic regression, chronic disease, scale of tumor, age, and ER expression affected the occurrence of lymph node metastases; the ORs were 3.05, 2.18, 0.34, and 3.83, respectively. Between different pathologic diagnoses and the risk factors, the OR scores were 12.7 and 8.02, respectively, for aggressive ductal carcinoma and aggressive lobular carcinoma auxiliary lymph node metastases. Conclusion: The incidence of lymph node metastases is affected by chronic disease, scale of tumor, age, ER expression and pathologic diagnosis.

Keywords: Primary breast cancer - metastasis to lymph nodes

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Introduction

Breast cancer is one of the primary cancers that endanger the health of women, which shows a rising trend every year. In Europe and in other developed countries, the incidence of primary breast cancer has made it the most common female cancer (Radice et al., 2003; Anderson et al., 2008; Porter, 2008; Mamounas, 2009; Wildiers et al., 2009; Hooks, 2010). As the economy of China develops and the standard of living improves, the incidence of primary breast cancer increases annually. Based on the "Chinese Breast Disease Survey Report" published by China Population Association on February 1, 2010, the incidence of female breast cancer in the major cities of China increased by 37%, and the mortality rate increased by 38.91% compared with that10 years ago (Zhang et al., 2006; Zhang et al., 2011). At present, the incidence rate of primary breast cancer in women tops the cancer list in Shanghai, Beijing, Guangzhou, and in other cities (Liu, 2011). Axillary lymph nodes are independent factors that determine breast cancer recurrence and prognosis; axillary lymph node transfer ratio and number can more clearly illustrate the extent of tumor invasion (Voordeckers et al., 2004). The survival rate after surgery without axillary lymph node metastasis after 10 years is 82%, whereas the rate of axillary lymph node metastasis is 39%. The total number of lymph nodes is closely related to the prognosis. The number of involved lymph nodes, especially in early cases, is closely related to prognosis. The 10-year survival rate of patients with metastases to 1-3 lymph nodes is 69%. The prognosis of patients with metastases to 4 or more lymph nodes is poor, the 10-year survival rate is only 20%, and the difference is significant. Among patients without lymph node metastasis, about 75% have no recurrence at 10 years, and 65% of cases with 1–3 positive lymph nodes and 85% of those with four or more, recur during local treatment after 10 years (Fisher et al., 2002; Voordeckers et al., 2004). In the present study, the factors that influence axillary lymph node metastasis in patients with breast cancer are discussed to determine their prognoses.

Materials and Methods

Samples

Up to 164 cases with primary breast cancer were randomly collected from January 2007 to December 2008 in the Guangzhou First People's Hospital. Cases that underwent surgery, chemotherapy, radiotherapy, or endocrine treatment were excluded. The diagnoses were based on the pathology report. All patients were admitted to the hospital with primary breast cancer, and then underwent radical surgery, hospitalization, or modified radical mastectomy.

Methods

The wax blocks containing the breast tumors obtained during the surgical removal were recollected and serially sliced into 3 μm sections. The expression

*[1]First Municipal Hospital of Guangzhou affiliated to Guangzhou Medical College, Guangzhou, [2]School of Public Health, Central South University, Changsha, China *For correspondence: lizhangchencn@126.com*

of estrogen receptors (ER), progesterone receptors (PR), and Cerb-2 were detected using surfactant protein immunohistochemical staining. The ER, PR, and Cerb-2 antibodies were obtained from Gene Co., Ltd., and the staining was carried out according to the manufacturer's instructions. Phosphate-buffered saline was used as the negative control for the primary antibodies, and a known positive biopsy of the kit was used as the positive control.

Results determination

The cell membrane or the cytoplasm exhibited brown-yellow granules, which were used as the positive criteria of the CerbB-2 protein. The nucleus exhibited brown-yellow granules, which were used as the positive criteria for the ER.

Ten high-power fields were selected in each slice, and 100 tumor cells were observed in each field. The average percentage of positive cells was calculated. The absence of positive cells or the presence of positive cells <10% were considered negative, 10%-25% positive cells were weakly positive (+), 26%-50% positive cells were positive (++), and positive cells >50% were strongly positive (+++). The positive and strongly positive cells were considered as CerbB-2 overexpression. Repeat detection was used whenever the results show ambiguity after discussion.

Statistical analysis

The SPSS 11.0 statistical software was used to establish the database and statistical analysis. The statistical methods used included chi square test to compare the parts of the group within the different age groups and the different types of chronic medical illness. The different types of tumor sizes, pathologies, ER expression on lymph node ratio, and the number of metastatic lymph nodes were compared. The effects of age, chronic disease, and CerbB-2 overexpression on the number of metastatic lymph nodes were analyzed using multi-factor variance analysis. The least significant difference (LSD) method was used in the pairwise comparison. The factors affecting axillary lymph node metastasis were analyzed by univariate and multivariate logistic regression backward stepwise regression (αenter = 0.05, αexcluded = 0.10). The level of significance was $\alpha = 0.05$ unless otherwise stated. All P values were indicated for bilateral probability in the present study.

Results

The oldest patient was 85 years old and the youngest was 26. Thus, the mean age was 57.8 ± 13.2 years old. The disease sites were all unilateral primary breast cancer including 83 cases on the left and 81 cases on the right side. Based on age, the site of the tumor in the different age groups showed no significant difference ($\chi^2 = 0.20$, P = 0.65). The diameter of the tumor was from 0.05 to 9.95 cm, with an average of 2.55 ± 1.41 cm and a median of 2.24 cm.

A total of 57 patients had varying degrees of chronic diseases, of which 40 cases had one disease, 11 had two diseases, and 7 had three diseases. Essential hypertension and type 2 diabetes were the most common medical conditions comprising 31 and 14 cases, respectively. The cases suffering from different chronic diseases were different in the different age groups. The prevalence among the 65 elderly patients was 64.3%, and compared with the younger age group (13.8%), the elderly patients were more likely to suffer from chronic diseases ($\chi^2 = 46.63$, P = 0.00).

Through pathology determination after the regional lymph node dissection, 88 patients had no axillary lymph node metastasis and 76 had varying degrees of regional lymph node metastasis, with metastasis rate of 46.3%. The possible influencing factors and assignments are shown in Table 1. If axillary lymph node metastasis is present, it was used as the dependent variable. The effects of the factors were analyzed by logistic regression univariate analysis, and a statistically significant variable ($\alpha = 0.10$ excluded) was screened (Table 2). Then, the resulting multiple variables were analyzed by logistic regression analysis using backward stepwise regression. Finally, six factors ($\chi^2 = 51.24$, P = 0.00) were obtained. In the model, chronicity, tumor size, ER expression, invasive ductal carcinoma, and invasive lobular carcinoma were considered risk factors, whereas age was a protective factor.

The number of axillary lymph nodes was 1-50, with an average of 11.9. The number of transfers was 1–25 months, with an average of 3.1. There was a high degree

Table 1. Six Possible Factors and the Assignment of Axillary Lymph Node

Variable code	Variable name	Assignment Description
Y	Lymph node metastassi	No=0, Yes=1
X_1	Age group	1=less than 65 years,2=over than or equal to65 years
X_2	Chronic types	the actual type of chronic medical illness
X_3	Tumor size	Actual tumor size
X_4	Invasive ductal carcinoma	No=0, Yes=1
X_5	Invasive lobular carcinoma	No=0, Yes=1
X_6	ER expression	1=negative, 2=positive

Table 2. The Estimates Value of Independent Variables into the Equation and Related Parameters

	b	S_b	Wald	P	OR	OR 95% confidence interval	
						Lower level	Upper level
Constant	-5.49	1.33	17.04	0	0		
X_1 (Age group)	-1.07	0.46	5.51	0.02	0.34	0.14	0.84
X_2 (Chronic type)	1.12	0.32	11.94	0	3.05	1.62	5.75
X_3 (Tumor size)	0.78	0.18	17.79	0	2.18	1.52	3.12
X_4 (Invasive ductal carcinoma)	2.54	0.8	10.23	0	12.72	2.68	60.49
X_5 (Invasive lobular carcinoma)	2.08	0.86	5.83	0.02	8.02	1.48	43.54
X_6 (ER expression)	1.34	0.41	10.54	0	3.83	1.7	8.62

Note: The control groups of X4, X5 were the special type of invasive carcinoma

Table 3. Comparison of Different Factors Affecting the Mean Number of Axillary Lymph Node Metastases

Chronic diseases types	CerbB-2 over-expression				
	Normal expression		Over-expression		
	<65 age	≥65 age	<65 age	≥65 age	Total
0	2.62	0.71	2.26	2.09	2.2
1	0.33	3.87	6.8	2.14	3.1
2	2.5	1.29	0	6	2.36
3	0	9.2	0	12	10
Total	2.36	2.85	3	3.07	2.76

of consistency between the lymph node metastatic ratio and the number of positive lymph nodes. The Spearman's rank correlation coefficient was 0.96 (P = 0.00). A tumor size of 2 cm was used as the critical value and the number of lymph node metastases of different sizes was compared. Significant differences were observed between the two groups (approximately $\chi^2 = 19.93$, P = 0.00). The tumors were larger, and the number of lymph node metastases was greater. Comparison of the lymph node metastatic ratio of the different tumor sizes showed a significant difference between the two groups (approximately $\chi^2 = 17.40$, P = 0.00). The greater the mass, the higher the transfer rate. Comparison of the different pathologic types and the axillary lymph node metastatic ratio was statistically significant ($\chi^2 = 6.66$, P = 0.04; $\chi^2 = 7.25$, P = 0.03). The rate of negative ER expression among the cases with axillary lymph node metastasis was 63.8%, which was higher than the positive expression (46.3%). The metastatic rate of the axillary lymph node among the different ER expression groups was significantly different ($\chi^2 = 8.06$, P = 0.04). The number of axillary lymph node metastasis and ER expression in the age group had no significant difference (Z value = -0.41, P = 0.68; $\chi^2 = 4.90$, P = 0.18).

The age group, chronic disease categories, and CerbB-2 overexpression were used as processing factors to compare the axillary lymph node metastases. The number of axillary lymph nodes influenced by the three factors were different (F = 4.98, P = 0.03).

Using the LSD method for pairwise comparison, the number of lymph node metastasis in the group number of chronic diseases was 3, which was statistically significant compared with that of the other three groups (P < 0.05). There were no significant differences (P > 0.05) among the other groups (Table 3). The number of metastatic lymph nodes in the old and the CerbB-2 overexpression groups, as well as that in the group with most number of chronic diseases were highest.

Discussion

The present study found that age is a protective factor for axillary lymph node metastasis. Furthermore, the degree of breast cancer differentiation among the elderly patients was relatively high, the degree of malignancy was relatively low, and the prognosis was good. Breast cancer is a hormone-related disease, and the hormone levels of the body change with age(Pierga et al., 2004; Louwman et al., 2007; Mamounas, 2009), which is one of the important causes of breast cancer fluctuations.

Chronic medical diseases, such as cardiovascular disease, diabetes, and chronic lung disease, are more common in elderly patients, next to hypertension and diabetes. Chronic diseases bring anesthesia risk, which affects the healing of incisions. Chronic diseases are risk factors for axillary lymph node metastasis, which suggests that the presence of chronic disease may induce patients to have a negative attitude regarding their disease, leading to delayed medical treatment.

ERs, which regulate breast cell growth and differentiation, are present in normal breast epithelial cell nuclei (Li et al., 2010; Li and Chen, 2010). In the present study, ER expression was found to be a risk factor for the incidence of axillary lymph node metastasis. However, the young breast cancer patients with high transfer rates showed a low strongly positive ER proportion, which caused some contradictions between them. These findings suggest that the differentiation in elderly patients was good, but that the tumors of the elderly breast cancer patients were not found early enough, thereby delaying treatment.

Compared with a special type of breast cancer, invasive ductal carcinoma and invasive lobular are more prone to axillary lymph node metastasis. The corresponding OR values were as high as 12.72 and 8.02, respectively, which may indicate that the invasive tumor growth cycle is longer. The patients were treated when more tumor masses formed. The incidence of the special type is relatively high among the pathologic types in the old breast patients, which further suggests a higher degree of differentiation among breast cancer in the elderly (Yu et al., 2010). CerbB-2, also known as HER-2 and neu, is a member of the epidermal growth factor receptor family that is involved in the regulation of cell growth, proliferation, and differentiation of tumor cells. Positive CerbB-2 expression in cancer cells indicates strong proliferative ability, rapid disease progression, short survival time; it is therefore an important early indicator of poor prognosis and metastasis of breast cancer (Bartlett et al., 2007; Azizun-Nisa et al., 2008). Whether CerbB-2 overexpression affects axillary lymph node metastasis remains unknown. However, CerbB-2 overexpression interacts with age and type of chronic disease to influence axillary lymph node metastasis. The incidence of axillary lymph node metastasis is greater in groups with high CerB-2 overexpression, which suggests that the presence of confounding factors influence the result to a certain extent.

Axillary lymph node metastasis is affected by many factors, and the factors interact. The presence of axillary lymph node metastasis determines the prognosis of patients, affects the treatment options, well as the attitude of patients.

Therefore, when determining the disease status of breast cancer patients, the development of specific surgical options, and the disease itself, the age of the patient, concomitant diseases, and other conditions should be considered, as well as when deciding on the appropriate surgical and postoperative treatment. Particular focus should be given for young age, tumor size greater than 2 cm, negative ER expression, and CerbB-2 overexpression.

Considering the high incidence of lymph node metastasis, radical surgery or modified radical mastectomy should be used. For elderly patients with small tumors, ipsilateral mastectomy or lumpectomy may be used as surgical approaches to reduce postoperative recovery time or because of the physical condition of the patient (Martín et al., 2009).

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