

Rate of Metastasis in Examined Lymph Nodes as a Predictor of Extracapsular Extension in Patients with Axillary Node-positive Breast Cancer

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Abstract

Background: The status of the axillary lymph nodes is an important factor in the prognosis and treatment of breast cancer. Extracapsular extension (ECE) is the spread of lymphatic tumor cells beyond the capsule of an axillary lymph node. Recent studies have demonstrated that ECE is a strongly unfavorable prognostic factor.

Objective: In the present study, we investigated whether the rate of metastasis among examined lymph nodes can be used to predict ECE in patients with axillary node-positive breast cancer.

Methods: The subjects were 95 women with axillary node-positive breast cancer. The numbers of lymph nodes removed (examined) and lymph nodes involved were recorded. The cut-off values, area under the curve, sensitivity, and specificity were calculated with the receiver operating characteristic curve technique for ability of the rate of metastasis to examined lymph nodes to predict ECE.

Results: The rate of metastasis to examined lymph nodes was significantly greater in patients with ECE than in patients without ECE [0.57 (0.03–1.00) vs. 0.22 (0.04–1.00), respectively, $p: 0.001$]. Similarly, the presence of vascular infiltration was significantly higher in patients with ECE than in those without ECE [30 (73.2%) vs. 25 (47.2%) respectively, $p: 0.010$]. On the other hand, other variables did not differ between the groups ($p > 0.05$). When the cut-off value was ≥ 0.23 , the sensitivity and specificity of the rate of metastasis to examined lymph nodes were 80.49% and 55.56%, respectively. The area under the curve was 0.697 (95% confidence interval: 0.594–0.787, $p: 0.004$).

Conclusion: Our results suggest that rate of metastasis among examined lymph nodes is a predictor of ECE in patients with axillary node-positive breast cancer.

(J Nippon Med Sch 2014; 81: 372–377)

Key words: axillary lymph node involvement, breast cancer, extracapsular extension, rate of metastasis among examined lymph nodes

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Journal Website (<http://www.nms.ac.jp/jnms/>)

Introduction

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death in women worldwide. In the United States, breast cancer is the most common cancer in women, the second most common cause of cancer death in women, and the main cause of death in women aged 20 to 59 years^{1,2}.

The status of the axillary lymph nodes is an important factor in the prognosis and treatment of breast cancer³. The absence of nodal involvement (N0) is an independent prognostic factor in breast cancer and is associated with a higher survival rate⁴. In addition, a significant negative association between the number of positive axillary nodes and survival has been reported⁵.

Extracapsular extension (ECE) is the spread of lymphatic tumor cells beyond the capsule of an axillary lymph node⁶. Recent studies have demonstrated that ECE is a strongly unfavorable prognostic factor⁷.

In this study, we investigated whether the rate of metastasis among examined lymph nodes can be used to predict ECE in patients with axillary node-positive breast cancer.

Materials and Methods

The subjects evaluated were 153 women who were operated on for breast cancer from 2008 through 2013 at our center and for who data was available. Patients with distant metastases and those without axillary lymph node involvement were excluded. The final group of subjects were 95 consecutive female patients with axillary node-positive breast cancer. The numbers of lymph nodes removed (examined) and of lymph nodes involved for each patient were recorded as evaluating pathology reports. The rate of metastasis among examined lymph nodes was calculated for each patient. We recorded biochemical measurements before surgery. We also noted demographic data, such as age. Tumors were graded according to the Modified Bloom-Richardson classification system.

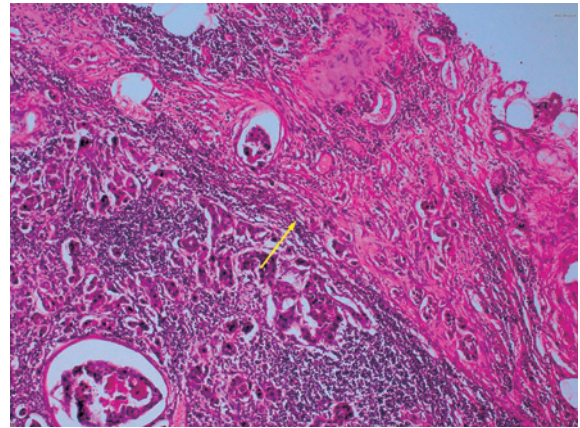


Fig. 1 Photomicrograph showing extracapsular extension in a patient with breast cancer (Hematoxylin-eosin stain, $\times 10$).

Primary tumor sizes were evaluated in 4 groups (T1, T2, T3, and T4), as stated in the TNM staging system. ECE was defined as the spread of lymphatic tumor cells beyond the capsule of an axillary lymph node (**Fig. 1**).

Formalin-fixed, paraffin-embedded tissues were immunohistochemically stained with CD 34. Lymphatic invasion was defined as the invasion by tumor cells of lymphatic vessels that were tortuous, thin-walled, and lacked a muscular layer. In tumoral areas, vascular invasion was prominent in thick-walled vessels with a distinctive muscular layer.

Statistical Analysis

Statistical analysis was performed with the software program SPSS for Windows 16.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine the normality of the distribution of variables. Continuous variables with normal distribution are presented as means \pm SD. The median value was used when distribution was not normal. Statistical analysis for parametric variables was performed with Student's *t*-test between groups. The Mann-Whitney U test was used to compare nonparametric variables between groups. The qualitative variables are given as percentages, and the correlation between categorical variables was investigated with the χ^2 test. The cut-off values, area under the curve (AUC), sensitivity, and specificity were calculated with the receiver operating characteristic (ROC) curve technique for

Table 1 Characteristics of 95 patients with nonmetastatic axillary node-positive breast cancer

Characteristic	
Age (years)	57.9 ± 12.3
Surgery	
Modified radical mastectomy	92 (96.8%)
Breast-conserving surgery with axillary lymph node dissection	3 (3.2%)
Histological type	
Invasive ductal carcinoma	90 (94.7%)
Invasive lobular carcinoma	2 (2.1%)
Invasive ductal and invasive lobular (mixed) carcinoma	1 (1.1%)
Other types of breast cancer	2 (2.1%)
Grade	
I	13 (13.7%)
II	42 (44.2%)
III	40 (42.1%)
T status	
T1	8 (8.4%)
T2	61 (64.2%)
T3	18 (18.9%)
T4	8 (8.4%)
Presence of lymphatic infiltration	28 (29.5)
Presence of vascular infiltration	55 (58.5)
Number of examined lymph nodes	17 (3–49)
Number of metastatic lymph nodes	5 (1–40)
Rate of metastasis among examined lymph nodes	0.33 (0.03–1.00)

the rate of metastasis among examined lymph nodes. *P*-values of <0.05 were considered statistically significant.

Results

Table 1 shows the characteristics of 95 patients with nonmetastatic axillary node-positive breast cancer. Mean age was 57.9±12.3 years (range, 38–89 years). The surgical treatment for most patients was modified radical mastectomy. The major histological type of breast cancer was invasive ductal carcinoma. The rate of metastasis among examined lymph nodes was 0.33 (range, 0.03–1.00). ECE was found in 41 (43.2%) patients.

Demographic, clinical, and histopathological variables of the 41 patients with ECE were compared with those of 54 patients without ECE (**Table 2**). The number of examined lymph nodes, number of metastatic lymph nodes, and rate of metastasis among examined lymph nodes were significantly greater in patients with ECE than in those without ECE (*p*: 0.001, <0.001, and 0.001,

respectively). Similarly, the rate of vascular infiltration was significantly greater in patients with ECE than in those without ECE (*p*: 0.010). On the other hand, the groups did not differ significantly in terms of age, T status, tumor grade, or presence of lymphatic infiltration (*p*>0.05).

The predictive role of rate of metastasis among examined lymph nodes in ECE was measured with ROC analysis. The sensitivity, specificity, positive and negative likelihood ratios, cut-off value, and positive and negative predictive values of the rate of metastasis among examined lymph nodes are shown in **Table 3**. When the cut-off level for the rate of metastasis among examined lymph nodes was ≥0.23, the sensitivity and specificity were 80.49% and 55.56%, respectively. The AUC was 0.697 (95% confidence interval: 0.594–0.787, *p*: 0.004) (**Fig. 2**).

Discussion

The status of the regional lymph nodes is an important prognostic factor in breast cancer². The absolute number of pathologically involved lymph

Table 2 Comparison of demographic, clinical, and histopathological variables in patients with and patients without extracapsular extension

Variable	Extracapsular extension present (n=41)	Extracapsular extension absent (n=54)	P value
Age (years)	56.1 ± 11.7	59.2 ± 12.7	0.233
Number of examined lymph nodes	20 (7-49)	15 (3-31)	0.001
Number of metastatic lymph nodes	10 (1-40)	3 (1-20)	<0.001
Rate of metastasis among examined lymph nodes	0.57 (0.03-1.00)	0.22 (0.04-1.00)	0.001
T status			0.799
T1 (%)	4 (9.8)	4 (7.4)	
T2 (%)	24 (58.5)	37 (68.5)	
T3 (%)	9 (22.0)	9 (16.7)	
T4 (%)	4 (9.8)	4 (7.4)	
Tumor grade			0.733
Grade 1 (%)	5 (12.2)	8 (14.8)	
Grade 2 (%)	20 (48.8)	22 (40.7)	
Grade 3 (%)	16 (39.0)	24 (44.4)	
Presence of lymphatic infiltration	14 (34.1)	14 (25.9)	0.259
Presence of vascular infiltration	30 (73.2)	25 (46.3)	0.010

Table 3 Cut-off value, sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values of the rate of metastasis among examined lymph nodes

	Cut-off value	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value	Negative predictive value
Rate of metastasis among examined lymph nodes	0.23	80.49	55.56	1.81	0.35	57.9	78.9

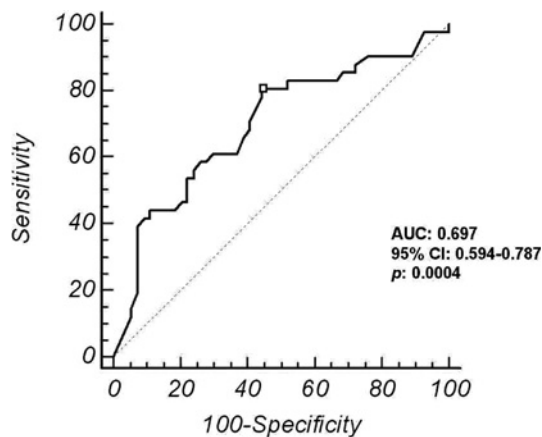


Fig. 2 ROC analysis of rate of metastasis among examined lymph as a predictor of extracapsular extension.

nodes has been reported to be an important prognostic factor in breast cancer⁸. More recent studies, however, have shown that the rate of involved axillary lymph nodes among lymph nodes examined better predicts prognosis than does the

absolute number of involved axillary nodes^{9,10}.

ECE is closely associated with prognosis in patients with breast cancer. Neri et al. have demonstrated that the survival rate is significantly lower for breast cancer with ECE than for breast cancer without ECE and has been identified with multivariate analysis as an independent negative prognostic factor on overall survival in patients with ECE⁷. Ilknur et al. have found with multivariate analysis that ECE has significant effects on both disease-free survival and distant metastasis-free survival¹¹.

In the present study, we found that ECE was present in 43.2% of the 95 patients. The percentage is an intermediate value among percentages reported in the literature, which range from 28% to 58%^{6,7,11-13}. Interestingly, we observed no significant difference between patients with ECE and those without ECE in terms of T status and tumor grade.

Recently, Gorgulu et al. have found that ECE is

associated with an increased rate of metastasis to examined lymph nodes in axillary node-positive breast cancer⁶. The rate was significantly higher in patients with ECE than in those without ECE. On the other hand, they did not indicate a specific cut-off point for the rate to predict ECE. In the present study, we also found that the rate of metastasis was significantly higher in patients with ECE than in those without ECE. In addition, we found that the sensitivity and specificity of the rate of metastasis to examined lymph nodes were 80.49% and 55.56%, respectively, when the cut-off level was a rate ≥ 0.23 . The AUC was 0.697 (95% confidence interval: 0.594–0.787, p : 0.004). Therefore, a rate ≥ 0.23 was used to predict ECE in patients with axillary node-positive breast cancer.

The number of examined lymph nodes was significantly higher in patients with ECE than in those without ECE. This difference appears to be due to the surgical approach based on the presence of ECE. Therefore, patients without ECE might undergo less extensive axillary dissection, and those with ECE might undergo more aggressive surgery.

Vascular invasion has independent significance for both survival and for local recurrence of tumor in patients with breast cancer; these patients showing no vascular invasion have a significant survival advantage and a reduced risk of local recurrence¹⁴. Similarly, lymphatic invasion is a strong prognostic factor for patients with breast cancer. In both lymph node-negative and lymph node-positive patients with breast cancer, lymphatic invasion indicates a high risk of death¹⁵. It is not surprising that in the present study the rate of vascular infiltration was significantly higher in patients with ECE than in those without ECE. Similarly, lymphatic infiltration was more frequent, but not significantly so, in patients with ECE than in patients without ECE.

Axillary lymph node dissection of at least level I or II, resulting in the examination of at least 10 lymph nodes by pathologists, has been shown to provide excellent prognostic information on nodal status and axillary tumor control in exchange for increased morbidity, which is a particularly high price to pay for node-negative patients^{16,17}. During surgery, however, suspected gross nodal disease

in level II or III is encountered, level III lymph node dissection is mandatory to increase regional control^{18–20}. Sometimes, adequate lymph node dissection is not performed. In such patients with breast cancer, the rate of metastasis among all nodes examined may be a useful prognostic variable.

In conclusion, our results suggest a relationship between ECE and the rate of metastasis among examined lymph nodes and that the rate is a strong predictor of ECE in patients with axillary node-positive breast cancer. This rate may be a useful variable in patients with breast cancer who do not undergo adequate lymph node dissection.

Conflict of Interest: The authors declare no conflict of interest.

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(Received, March 12, 2014)

(Accepted, August 20, 2014)