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Predictive Factors Affecting Axillary Lymph Node Metastasis in Breast Cancer

Meme Kanserinde Aksilla Metastazini Etkileyen Prediktif Faktörler

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Abstract

Aim: The status of axillary lymph node metastasis (ALNM) at diagnosis has been considered as one of the most important prognostic factors for overall and disease-free survival in patients with breast cancer. Determination of breast cancer patients at risk for ALNM is important for treatment planning. The purpose of this study was to determine the factors that affect axillary lymph node involvement in breast cancer in addition to biological and pathological parameters to prevent unnecessary lymph node dissections.

Methods: Immunohistochemical and pathologic features of 131 breast cancer patients, who underwent breast surgery, were investigated retrospectively.

Results: ALNM was detected in 60% (n=79) of patients. In univariate analysis, histological grade, tumor size, lymphovascular invasion, perineural invasion, HER2 positivity and large intraductal component were found to be high risk factors for ALNM. In multivariate analysis, increased tumor size (T1; OR: 0.2, p<0.034) and presence of lymphovascular invasion (OR: 0.2, p<0.001) were found to be independent factors for ALNM.

Conclusion: In our study, presence of lymphovascular invasion and increased tumor size were found to be independent predictive factors for axillary lymph node involvement. In univariate analysis, histological grade, tumor size, lymphovascular invasion, perineural invasion, HER2 positivity and large intraductal component were found to be high risk factors for ALNM. Patients carrying these factors may be included in the higher risk group for lymph node involvement. However, more data is needed to identify the factors that may help to decide for axillary lymph node dissection.

Keywords: Axillar, breast, cancer, lymph node

Öz

Amaç: Aksiller lenf nodülü metastazının (ALNM) tanı anındaki durumu, meme kanseri olan hastaların genel ve hastalıksız sağkalımı için en önemli prognostik faktörlerden biri olarak kabul edilmiştir. ALNM riski taşıyan meme kanseri hastalarının belirlenmesi, tedavi planı için önemlidir. Bu çalışmamızın amacı meme kanserinde aksiller lenf nodu tutulumunu etkileyen faktörleri gereksiz diseksiyon yapılan hasta grubunu belirlemek idi.

Yöntemler: Meme kanseri nedeni ile cerrahi tedavi uygulanan 131 meme kanseri hastanın immünohistokimyasal ve patolojik özellikleri retrospektif olarak incelenerek kaydedildi.

Bulgular: ALNM hastaların %60'ında (n=79) saptanmıştır. Univariate analizde histolojik grade, tümör boyutu, lenfovasküler invazyon, perinöral invazyon, HER2 pozitifliği ve geniş intraduktal bileşen ALNM için yüksek riskli bulundu. Multivariate analizde, artmış tümör boyutu (OR: 0,2, p<0,030) ve lenfovasküler invazyon varlığı (OR: 0,2, p<0,001), pozitif ALNM için bağımsız faktörler olarak bulundu.

Sonuç: Çalışmamızda lenfovasküler invazyon varlığı, artmış tümör boyutu, aksiller lenf nodu tutulumu için bağımsız prediktif faktörler olarak bulundu. Univariate analizde histolojik grade, tümör boyutu, lenfovasküler invazyon, perinöral invazyon, HER2 pozitifliği ve geniş intraduktal bileşen ALNM için yüksek riskli bulundu. Bu faktörleri taşıyan hastalar, lenf nodu tutulumu için daha yüksek risk grubuna dahil edilebilir, ancak aksiller lenf nodu disseksiyonu için karar vermede yardımcı olabilecek faktörleri tanımlamak için daha fazla veri gerekmektedir.

Anahtar Sözcükler: Aksilla, meme, kanser, lenf nodu

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Introduction

Today, the most important prognostic factor for breast cancer is the presence of axillary lymph node metastasis (ALNM) and the number of lymph nodes involved (1). If axillary lymph node involvement is absent, the 10-year disease-free life expectancy is 70-80%. However, the presence of axillary lymph node involvement drops the life expectancy to 30% (2,3). In almost all investigations, a direct correlation was found between the number of nodes involved and the course of the disease (4). As the number of affected nodes increases, recurrence risk rises, prognosis becomes worse and the risk of treatment failure increases (5). Axillary lymph node dissection (ALND) is needed for definitive staging. However, it is not necessary in cases where unnecessary dissection may increase morbidity (1). The extent of dissection required for staging is to determine the nodal involvement and the number of lymph nodes retained (1). Complications such as pain, lymphedema, and nerve damage may lead to hesitation for ALND (6). However, axillary staging is considered mandatory in the treatment of breast cancer (7). The specificity and sensitivity of manual examination is low (8). With the introduction of the sentinel lymph node biopsy (SLNB) technique in surgical practice, the views on ALND have changed and complications have reduced. SLNB became standard in patients with negative lymph nodes (9). SLNB requires a multidisciplinary team, an operating room and a long time and has a false negative rate of 15-20% in frozen section (10). These are undesirable features. However, there is no doubt for SLNB today. If the lymph node involvement is correctly detected before the surgery, unnecessary ALND may be avoided. Our aim in this study was to identify some demographic, biochemical, and pathologic parameters that affect axillary lymph node involvement and in this way, to reduce the rate of ALND.

Methods

Patients and Tumor Characteristics

A total of 131 patients, who had undergone surgery due to breast cancer in Haseki Training and Research Hospital between March 2009 and August 2014, were included in this study. Results of the pathological investigations and other identical and biochemical data were analyzed. Ethics committee approval was taken prior to the examination of the records (No: 561). The pathology records and treatment charts of 131 patients were retrospectively reviewed and the patient and tumor characteristics were recorded. The histopathological features we evaluated were tumor size, histological grade (1-3), lymphovascular invasion, perineural invasion, estrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2)/neu expression, Ki-67 proliferation index, extensive intraductal component (EIC), and axillary lymph node involvement.

To choose the best protocol for treatment, EIC, which is ductal carcinoma *in situ* (DCIS), must occupy greater than 25% of all the area encompassed by the whole infiltrating tumor and DCIS present in grossly normal adjacent breast tissue. If the intraductal tumor is greater than 25% of the whole tumor, mastectomy must be considered and, in this case, breast-conserving surgery should not be performed. The threshold value for Ki-67 index was accepted as 14%.

Statistical Analysis

The IBM SPSS Statistics 22.0 for Windows package program was used to analyze the data (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentages. Categorical variables between the two groups were compared with the chi-square test. The Pearson's correlation coefficient was used for correlation analysis. Univariate analysis (chi-square test or Fisher's exact test) was used to assess the relationship between clinical and pathological variables and ALNM status. Multivariate logistic regression analysis was performed to adjust the relationship between clinical and pathological variables and ALNM status according to other factors. Adjusted ORs, 95% CIs and p values are presented. A p value of less than 0.05 was considered statistically significant.

Results

The patient and tumor characteristics are shown in Table 1. One hundred and thirthy-one patients (four men, 127 women) were enrolled in this study. The mean age was 57.8±12.2 years (median=52 years, range=33-92 years). Invasive ductal carcinoma was the most common tumor type (78%). Other types were invasive lobular carcinoma, mixed tumors, mucinous breast carcinoma, medullary breast carcinoma, and intracystic papillary carcinoma. The mean number of total lymph nodes removed was 15.3±7.4. There were 33 (25.1%) patients with T1 tumor, 52 (39.6%) with T2 tumor, 28 (21.3%) with T3 tumor and 18 (13.7%) patients with T4 tumor.

Histologic grade ($p<0.005$), tumor diameter ($p<0.007$), perinural invasion ($p<0.011$), lymphovascular invasion ($p<0.001$), HER2 positivity ($p<0.014$), EIC ($p<0.013$), ER/PR/HER2 subgroups ($p<0.041$) and number of total lymph nodes ($p<0.001$) were significantly higher in ALNM-positive patients compared to ALNM-negative patients. However, no significant difference was found between the two groups in terms of age, gender, tumor type, ER status, PR status, and Ki-67 proliferation index (Table 1).

Univariate analysis was performed to determine the relationship between clinical and pathological variables

and ALNM status (Table 2). Six variables were significant in univariate analysis. These findings were lymphovascular invasion (OR: 0.230, p=0.001), perineural invasion (OR: 0.386, p=0.011), poor histologic grade (OR: 0.364, p=0.012), HER2 positivity (OR: 0.374, p=0.016), EIC (OR: 0.392, p=0.013) and tumor diameter (T1; OR: 0.188, p=0.021, T2; OR: 0.2, p=0.02). There was no relationship between ER/PR/HER2 subgroups and Ki-67 proliferation index and ALNM.

Multivariate logistic regression analysis was performed for the variables that were found to be statistically significant in the univariate analysis. The relationships between the six pathological factors and the ALNM status are shown in Table 3. Tumor size (OR: 0.2, p=0.03) and presence of lymphovascular invasion (OR: 0.2, p=0.001) were found to be independent predictors for ALNM.

Discussion

Tumor diameter is an important and reliable prognostic factor for the risk of relapse in breast cancer and has an important value in the choice of adjuvant treatment, especially in lymph node-negative patients (11). As the diameter increases, the number of axillary lymph nodes involved increases. Larger tumors are more aggressive.

Table 1. Patient and tumor characteristics (n=131)

Factor	Number	Nodule negative n=52	Nodule positive n=79	p
≤50 age	45	18 (34.6%)	27 (34.2%)	0.959
>50 age	86	34 (65.4%)	5 (265.8%)	
Female	127	52 (100%)	75 (94.9%)	0.099
Male	4	0 (0.0%)	4 (5.1%)	
Total number of lymph nodes	-	8.9±3.1	19.6±6.2	0.001
IDC	102	40 (76.9%)	62 (78.5%)	0.789
ILC	12	6 (11.5%)	6 (7.6%)	
ICPC	3	2 (3.8%)	1 (1.3)	
Medullary CA	3	1 (1.9%)	2 (2.5%)	
Mucinous CA	5	1 (1.9%)	4 (5.1%)	
Mixed	6	2 (3.8%)	4 (5.1%)	
Grade 1	20	4 (7.7%)	16 (20.3%)	0.005
Grade 2	61	33 (63.5%)	28 (35.4%)	
Grade 3	50	15 (28.8%)	35 (44.3%)	
T1	33	17 (32.7%)	16 (20.3%)	0.007
T2	52	26 (50%)	26 (32.9%)	
T3	28	6 (11.5%)	22 (27.8%)	
T4	18	3 (5.8%)	15 (19%)	
LVI	94	28 (53.8%)	66 (83.5%)	0.001
PNI	61	17 (32.7%)	44 (55.7%)	0.011
ER positive	106	42 (80.8%)	64 (81%)	0.972
PR positive	94	37 (71.2%)	57 (72.2%)	0.901
HER2 positive	44	11 (31.2%)	33 (41.8%)	0.014
ER/PR+, Her2-	74	36 (69.2%)	38 (48.1%)	0.041
ER/PR+, Her2+	35	7 (13.5%)	28 (35.4%)	
ER/PR-, Her2-	13	5 (9.6%)	8 (10.1%)	
ER/PR, Her2+	9	4 (7.7%)	5 (6.3%)	
Ki-67 positive	75	25 (48.1%)	50 (63.3%)	0.085
EIDC	58	16 (30.8%)	42 (53.2%)	0.013

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, ICPC: Intracystic papillary carcinoma, LVI: Lymphovascular invasion (positive), PNI: Perineural invasion (positive), EIDC: Extensive intraductal component (positive), ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2, CA: Carcinoma

In all the nodal involvement categories, life expectancy decreases as tumor diameter increases (12,13). In their study, Carter et al. (14) used data on 24740 cases of breast cancer recorded in the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, to evaluate 5-year relative survival rates. They found a significant relationship with tumor size and axillary lymph node involvement. In this study, increased tumor diameter was found to be an independent risk factor for axillary lymph involvement. In approximately 70% of patients with T1/T2 tumors, axillary lymph nodes do not contain tumor (15). The rate of axillary lymph node involvement is 0.1% for DCIS, 3-5% for T1 a tumor, 10-17% for T1b, and 23-45% for T2 tumors (16).

Table 2. Univariate analysis of factors associated with axillary lymph node metastasis

Factor	OR (95% CI)	p
Age groups		
≤50 age	-	0.959
>50 age	0.981 (0.470-2.049)	
Total number of lymph nodes	3.454 (0.780-5.406)	0.982
Histological grade		
Grade 1	1.714 (0.490-5.99)	0.399
Grade 2	0.364 (0.166-0.799)	0.012
Tumor size		
T1	0.188 (0.046-0.775)	0.021
T2	0.200 (0.052-0.774)	0.020
T3	0.733 (0.158-3.398)	0.692
LVI	0.230 (0.103-0.515)	0.001
PNI	0.386 (0.186-0.802	0.011
ER status	0.984 (0.404-2.397)	0.972
PR status	0.952 (0.438-2.068)	0.901
HER2 status	0.374 (0.168-0.834)	0.016
ER/PR+, Her2-	0.8440 (0.210-3.396)	0.812
ER/PR+, Her2+	3200 (0.677-15.136)	0.142
ER/PR-, Her2-	1280 (0.228-7.187)	0.779
Ki-67	0.537 (0.264-1.093)	0.086
EIDC	0.392 (0.188-0.818)	0.013

LVI: Lymphovascular invasion (positive), PNI: Perineural invasion (positive), EIDC: Extensive intraductal component (positive), HER2: Human epidermal growth factor receptor 2, ER: Estrogen receptor, PR: Progesterone receptor, OR: Odds ratio, CI: Confidence interval

Table 3. Multivariate logistic regression analysis showing independent predictive predictors of axillary lymph node metastasis

Factor	Odds ratio (95% CI)	p
Tumor size (T1)	0.2 (0.05-0.89)	0.034
Tumor size (T2)	0.2 (0.05-0.86)	0.030
Tumor size (T3)	0.9 (0.19-4.90)	0.974
Lymphovascular invasion	0.2 (0.08-0.49)	<0.001

CI: Confidence interval

The prognostic value of estrogen and progesterone receptors has been demonstrated in a group of neoplastic diseases, particularly in breast and endometrial carcinoma. ER- and PR-positive tumors respond better to hormone therapy and have better prognosis. 55-65% of primary breast cancer is ER-positive, and 40-60% is PR-positive (17,18). Knight et al. (19) have shown that ER were independent prognostic risk factor for early stage breast cancer and early recurrence. According to data from San Antonio and National Surgical Adjuvant Breast Cancer Project in 2002, the survival advantage was 10% in 5 years. ER is strongly related with cancer-free survival. PR is shown for better endocrine treatment response after recurrence and that is why more related to general survival than ER (20). It has been shown that neu oncogene (C-ERB2=HER2) was an important mediator of cell proliferation and differentiation (21). C-ERB2 positivity was high in histologic grade ER- and PR-negative, lymph node-positive and highly proliferative cancers (21,22).

Perou et al. (23) divided breast cancer into four categories according to their genomic properties and cyokeration structure. In 2001, Sorlie et al. (24) divided the tumors that have been classified as luminal type into two categories: Luminal A and Luminal B. These two molecular subtypes (Luminal A and B) are HER2-positive, basal-like, and normal breast-like tumors. Afterwards, another group, called claudin-low, was added as another subtype. It was also found in this study that there was no significant difference between molecular subtypes. On the other hand, HER2 positiveness was found to be significant for ALNM by using univariate analysis. However, ER and PR positiveness was found to be insignificant.

There is a lymphovascular invasion in one-third of breast neoplasms. Lymphovascular invasion is a negative prognostic factor. In a great deal of studies, it has been reported that lymphovascular invasion, tumor size, and histological grade were strongly associated with ALNM (25). In addition, perineural invasion is usually observed with lymphatic invasion (26).

Regardless of tumor size, EIC-positive tumors are associated with more frequent local recurrences. The 5-year-survival for EIC-positive and -negative tumors is 6% and 24%, respectively (27). Patients with extensive positive intraductal tumor and lymphovascular invasion were less frequently reported for negative surgical borders and higher local recurrences. Therefore, general and cancer-free survival percentages were shown lower in these

patients (28). In this study, EIC positivity was found to be a significant factor for the presence of axillary metastasis.

Azambuja et al. (29) conducted a meta-analysis of 46 studies involving 12,155 patients. They found that Ki-67/MIB-1 positivity was associated with higher probability of relapse and worse survival in node-negative and node-positive patients. This meta-analysis revealed the prognostic value of Ki-67. Tumors with high Ki-67 expression is more chemosensitive, nevertheless, they have poor prognosis. On the other hand, tumors with low Ki-67 expression are hormonesensitive and good prognosis tumors (30). In our study, Ki-67 proliferation index was not statistically significant. However, it was found to be higher in the ALNM-positive group (63.3%) than in the ALNM-negative group (48.1%).

In our study, it was found in univariate analysis that increased tumor diameter, poor histological grade, presence of lymphovascular invasion, perineural invasion, HER2 positivity, and EIC were important factors. In multivariate analysis, increased tumor size and presence of lymphovascular invasion at the time of diagnosis were independent predictive factors for ALNM. These findings were similar to those in several previous studies (26,31).

Conclusion

Tumor size and lymphovascular invasion and tumor characteristics were found to be independent factors and powerful predictors for risk of ALNM on the multivariate analysis for patients who underwent surgery for breast cancer.

Authorship Contributions

Concept: S.B. Design: S.B. Data Collection or Processing: S.B., C.T. Analysis or Interpretation: S.B., C.T. Literature Search: S.B., C.T. Writing: S.B.

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