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Impact of status of ER, PR, HER2 and Ki-67 index on axillary lymph node metastasis of breast cancer

Meme kanserinin aksiller metastazlarında ER, PR, HER2 ve Ki-67 indeksinin etkisi

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Abstract

Aim: Axillary status evaluation and, if present, the number of metastatic lymph nodes is important in staging and adjuvant therapy planning of breast cancer. A number of clinical and pathological variables were analyzed to detect factors affecting nodal status.
Methods: A total of 298 women with unilateral breast cancer operated with axillary lymph node dissection or sentinel lymph node biopsy, were retrospectively analyzed for age, localization, BIRADS category, pathological features, subtypes as Luminal A, Luminal B, HER2 positive, triple negative, Ki-67 index and number of lymph nodes involved.
Results: The mean age was 54.7 years. BIRADS 5 was the most detected category in 208 (69.8%) patients. The most common pathological type was invasive ductal carcinoma in 265 patients (88.9%). The most detected tumor grade was grade 2 in 160 (31.2%). Luminal B was the most common subtype and detected in 173 patients (58.1%). Ki-67 indexes were detected between 0-14% in 69 patients (23.3%), between 15-19% in 31patients (10.4%) and above 20% in 198 patients (66.4%).
Conclusions: HER2 positivity, Ki-67 index, and progesterone receptor negativity are the most significant factors affecting axillary lymph node metastasis.

Key Words: Breast cancer, axillary lymph node metastasis, hormonal status.

Öz

Amaç: Aksiller lenf nodu metastazı değerlendirmesi ve varsa lenf nodu sayısı meme kanserinin evrelemesi ve adjuvan tedavi planlamasında önemlidir. Amacımız lenf nodu metastazını etkileyen faktörleri saptamak için bir dizi klinik ve patolojik değişkeni araştırmaktır.
Yöntemler: Aksiller lenf nodu diseksiyonu veya sentinel lenf nodu biyopsisi ile opere edilen tek taraflı meme kanseri olan 298 kadın hastanın yaş, lokalizasyon, BIRADS kategorisi, patolojik özellikler, Luminal A, Luminal B, HER2 pozitif, tripl negatif subtipleri, Ki-67 indeksi verileri ile metastatik lenf nodu sayısı arasındaki ilişkisi analiz edildi.
Bulgular: Yaş ortalaması 54,7 yıl idi. BIRADS 5, 208 (% 69,8) hastada en fazla saptanan kategori idi. En sık görülen patolojik tip 265 hastada (% 88,9) invaziv duktal karsinomdu. En fazla saptanan tümör evresi 2 olup, 160 hastada (% 31,2) tespit edildi. Luminal B en sık görülen subtipti ve 173 (% 58,1) hastada tespit edildi. Ki-67 indeksi 69 hastada (% 23,3) % 0-14, 31 hastada (% 10,4) % 15-19 ve 198 hastada (% 66,4) % 20'nin üzerinde saptandı.
Sonuçlar: HER2 pozitifliği, Ki-67 indeksi ve progesteron reseptör negatifliği aksiller lenf nodu metastazını etkileyen en önemli faktörlerdir.

Anahtar Kelimeler: Meme kanseri; aksiller lenf nodu metastazı; hormonal durum

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Introduction

Breast cancer (BC) is one of the most common cancers in women and its incidence increases every year. The prognosis and life expectancy is closely related to axillary lymph node metastasis (ALM) and the number of metastatic lymph nodes. Axillary status is also important in staging and for planning postoperative chemoradiotherapy. Therefore, every effort should be done for accurate assessment of the axilla [1].

Hormonal receptor status of the tumor as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 proliferation index are important for ALM, subtyping and choice of treatment modality [1,2]. Other prognostic factors, also for ALM, are age, tumor subtypes as Luminal A (LA), Luminal B (LB), HER2 positive, and Triple negative (TN) according to St. Gallen Consensus 2013 [1, 3], histological and nuclear grade, tumor size, multifocality, lymphovascular invasion and the stage of the tumor [4,5].

The aim of this study is to find out the factors affecting the number of ALM in our series.

Material and methods

Our study was approved by the Haseki Research and Training Hospital Ethical Committee on October 10th, 2017/555 with full compliance to Helsinki declaration, as revised by 2000. Informed consent was obtained on the first day of hospitalization from all individual participants included in the study.

Age, localization, and BIRADS category reports were recorded. The axillary status evaluation was made by mammography, ultrasonography and, if needed, by other imaging modalities. A detailed pathological examination was made on the terms of type, tumor diameter, histological grade, lymphatic invasion, perineural invasion, number of metastatic lymph nodes (1-3, 4-9, >10), hormonal status as ER, PR, HER2, Ki-67 index analysis (in the range of 0-14, 15-19, >20 as percentages) and subtypes LA, LB, HER2 positive, TN.

Two hundred and ninety-eight BC cases operated with axillary lymph node dissection or sentinel lymph node biopsy (SLNB) between March 1st, 2009 and March 1st, 2017 were retrospectively analyzed. For the scope of this study, 298 BC patients met the inclusion criteria. The patients with male gender, bilateral BC, having other cancers previously or at the time of BC diagnosed, and the patients taking neoadjuvant chemotherapy were excluded.

All patients underwent local excision of the tumor or mastectomy according to tumor/breast ratio for better cosmetic results. Axillary lymph node dissection was done directly in patients with positive lymph nodes on imaging. SLNB was done in other patients. At least 3 lymph nodes were excised. If positive, they also underwent axillary dissection. If negative, they were accepted as ALM negative.

Outcomes were searched whether variables/parameters affect ALM and number of lymph nodes or not.

Statistical analysis

SPSS 15.0 (SPSS Inc. Chicago, USA) program for Windows was used for statistical analysis. Descriptive statistics, number and percentage for categorical variables, means, standard deviation, minimum, maximum for quantitative variables were given. To compare the rates in independent groups, the Chi-square test was used. Relations between ratios in groups were studied by linear-by-linear association. The relations of ordinal variables were analyzed by Spearman's correlation analysis. A p-value <0.05 was taken to be statistically significant.

Results

The results of demographic, radiologic and pathologic features of the patients are presented in Table 1 and Table 2.

Table 1: Demographic and pathologic features (N=298).

		n	%
Localization	Right	142	47.7
	Left	156	52.3
Type	Invasive ductal carcinoma	265	88.9
	Invasive lobular carcinoma	9	3.0
	Mucinous carcinoma	16	5.4
	Ductal carcinoma in situ (with invasive foci)	5	1.7
	Papillary carcinoma	3	1.0
Subtype	Luminal A	65	21.8
	Luminal B	173	58.1
	HER2 positive	27	9.1
	Triple negative	33	11.1
T stage	T1	92	30.9
	T2	168	56.4
	T3	30	10.1
	T4	8	2.7
Grade	1	45	15.1
	2	160	53.7
	3	93	31.2
BIRADS Category	0	27	9.1
	3	10	3.4
	4	32	10.7
	5	208	69.8
	6	21	7.0

Table 2. Detailed pathological examination.

		n	%
Metastatic lymph node	Negative	141	47.3
	≤3 positive	104	34.9
	4-9 positive	32	10.7
	10 and more	21	7.0
Lymphatic Invasion	Yes	200	67.1
Perineural Invasion	Yes	145	48.7
Estrogen Receptor	Positive	240	80.5
Progesterone Receptor	Positive	229	76.8
HER2	Positive	86	28.9
Ki-67 index (percentage)	0-14	69	23.2
	15-19	31	10.4
	20 and more	198	66.4

Table 3. Correlation of clinical parameters and axillary lymph node metastasis relationship.

		Metastatic lymph node (n(%))				
		Negative	≤3 positive	4-9 positive	>10 positive	p
Localization	Right	62 (44.0)	53 (51.0)	19 (59.4)	8 (38.1)	0.289
	Left	79 (56.0)	51 (49.0)	13 (40.6)	13 (61.9)	
Type	Invasive ductal	126 (89.4)	91 (87.5)	28 (90.3)	20 (95.2)	0.985
	Invasive lobular	4 (2.8)	5 (4.8)	0 (0)	0 (0)	
	Mucinous	8 (5.7)	5 (4.8)	2 (6.5)	1 (4.8)	
	Ductal Carcinoma in Situ (with invasive foci)	2 (1.4)	2 (1.9)	1 (3.2)	0 (0)	
	Papillary	1 (0.7)	1 (1.0)	1 (0.03)	0 (0)	
Subtype	Luminal A	35 (24.8)	20 (19.2)	6 (18.8)	4 (19.0)	0.062
	Luminal B	81 (57.4)	58 (55.8)	24 (75.0)	10 (47.6)	
	HER2 Positive	12 (8.5)	8 (7.7)	2 (6.3)	5 (23.8)	
	Triple Negative	13 (9.2)	18 (17.3)	0 (0)	2 (9.5)	
T stage	T1	55 (39.0)	17 (16.3)	14 (43.8)	6 (28.6)	0.927 *
	T2	67 (47.5)	72 (69.2)	14 (43.8)	15 (71.4)	
	T3	14 (9.9)	12 (11.5)	4 (12.5)	0 (0)	
	T4	5 (3.5)	3 (2.9)	0 (0)	0 (0)	
Grade	1	12 (15.6)	15 (14.4)	8 (25.0)	0 (0)	0.736 *
	2	69 (48.9)	65 (62.5)	15 (46.9)	11 (52.4)	
	3	50 (35.5)	24 (23.1)	9 (28.1)	10 (47.6)	
BIRADS	0	11 (7.8)	10 (9.6)	5 (15.6)	1 (4.8)	0.570 *
	3	5 (3.5)	5 (4.8)	0 (0)	0 (0)	
	4	20 (14.2)	12 (11.5)	0 (0)	0 (0)	
	5	95 (67.4)	73 (70.2)	24 (75.0)	16 (76.2)	
	6	10 (7.1)	4 (3.8)	3 (9.4)	4 (19.0)	

* Linear-by-Linear Association

All of the patients were women with unilateral breast cancer. The mean age was 54.7 ± 12.9 years (range: 27-92). BIRADS 5 category was the most commonly observed category with a rate of 69.8% in 208 patients. Invasive ductal carcinoma was detected in 265 (88.9%). The most common tumor diameter detected was T2 in 168 patients (56.4%).

Mean harvested lymph node number in axillary dissection was 15 (range 13-17). Axillary status was negative in 141 (47.3%) patients and positive in 157 patients (52.7%). Positive metastatic lymph nodes were 3 or less in 104 patients (34.9%), between 4 to 9 in 32 (10.7%) and 10 or more in 21 patients (7.0%). Molecular subtype luminal B had the highest number in 173 patients (58.1%).

The results of statistical analysis between parameters and ALM are shown in Table 3 and 4.

Table 4. Correlation of tumoral parameters and axillary lymph node metastasis.

		Metastatic lymph node (n(%))				
		Negative	<3 positive	4-9 positive	>10 positive	p
Lymphatic invasion	Yes	82 (58.2)	84 (80.8)	22 (68.8)	12 (57.1)	0.243*
	No	59 (41.8)	20 (19.2)	10 (31.3)	9 (42.9)	
Perineural invasion	Yes	59 (41.8)	55 (52.9)	21 (65.6)	10 (47.6)	0.065*
	No	82 (58.2)	49 (47.1)	11 (34.4)	11 (52.4)	
Estrogen receptor	Positive	117 (83.0)	78 (75.0)	32 (100.0)	13 (61.9)	0.419*
	Negative	24 (17.0)	26 (25.0)	0 (0)	8 (38.1)	
Progesterone receptor	Positive	114 (80.9)	80 (76.9)	24 (75.0)	11 (52.4)	0.012*
	Negative	27 (19.1)	24 (23.1)	8 (25.0)	10 (47.6)	
HER 2	Positive	31 (22.0)	23 (22.1)	19 (59.4)	13 (61.9)	<0.001 *
	Negative	110 (78.0)	81 (77.9)	13 (40.6)	8 (38.1)	
Ki-67 index	0-14 %	50 (35.5)	17 (16.3)	2 (6.3)	0 (0)	<0.001 *
	15-19%	22 (15.6)	6 (5.8)	1 (3.1)	2 (9.5)	
	>20 %	69 (48.9)	81 (77.9)	29 (90.6)	19 (90.5)	

* Linear-by-Linear Association

There was no significant difference for the number of ALM affected by tumor type, tumor diameter, histological grade and molecular subtypes (p=0.886, p=0.927, p=0.736 and p=0.062, respectively). The presence of lymphovascular invasion and perineural invasion were detected in 200 (67.1%) and 145 patients (48.7%), respectively. But both were not found to increase significantly ALM (p=0.243 and p=0.065, respectively).

HER2 receptor was positive in 86 patients (28.9%) and negative in 212 (71.1%). Ki-67 proliferation index was found to be in the range of 0-14% in 69 patients, in 31 patients (10.4%) in the range of 15-19% and in 198 patients (66.4%) in the range of >20%. Most of the patients were in the range of >20%. PR was positive in 229 (76.8%) and negative in 69 patients (23.2%). ER positivity was seen in 240 patients (80.5%).

Statistical analyses resulted as HER2 positivity, Ki-67 index and PR negativity increase the number of ALM showing a statistically significant difference (p<0.001, p<0.001 and p=0.012, respectively).

Discussion

In this study, we present an article to find out which factors affect ALM in BC patients in our series. ALM is important for expected survival rate. If predictive variables for axillary involvement are known, the treatment may be more specific and oncologic safety is maintained as well as surgical morbidity. Similar articles in the literature give various factors and their effects.

There was no significant difference for ALM and number of lymph nodes affected among any of the tumor types (p=0.886). The most detected tumor type was invasive ductal carcinoma (89.9%). This result was consistent with some

literatures [3, 6, 7] and inconsistent with some of the literature with the largest population of breast cancer series [1, 8]. 623 and 380 patients were included in these two published studies, respectively, and they found tumor type-histology was significantly related to ALM ($p<0.001$ and $p=0.003$, respectively). Tumor diameter (T1-T4) was not found to have an effect for ALM significantly in our series. In fact, it is logic to think, as the tumor size increases, ALM occurs more, especially with the existence of lymphovascular invasion. So, this result was found in the literature [1, 8, 9]. Lymphovascular invasion was found in 67.1% of the patients in this study, but it was not significant for ALM, whereas it is claimed that lymphovascular invasion is significantly associated with ALM [4]. Grade 2 was the most commonly found histological in our study. But, the grade of the tumor was not correlated with ALM significantly.

Hormonal receptor status and Ki-67 proliferation index are studied for biological behavior of primary tumor [3]. Related to ER, PR, HER2, and Ki-67 index, molecular subtypes LA, LB, HER2 positive, and TN are formed. Most studies demonstrated that ER, PR, HER2, Ki-67 provided independent prognostic information in BC patients [10]. In our study, we didn't find such correlation between subtypes and ALM.

PR, HER2 and Ki-67 are mostly discussed for ALM and choosing treatment modalities. There are disagreements for progesterone receptor status correlation with ALM in the literature. Tan et al. [8] found a correlation between progesterone receptor positivity and lymph node metastases. Also, some other authors [11, 12] claimed this association. Viale et al. [13] demonstrated an inverse relationship, some studies showed no correlation [14]. Progesterone receptor expression negativity significantly affected ALM in our study.

HER2 is related with tumor proliferation and tumor progression. For ALM, its status is controversial. In the study of Emma Aitken et al. [1], no significant association was found for HER2 status with ALM. In our study, HER 2 was positive in 28.9% of the patients and negative in 71.1%. Its expression demonstrated a statistical significance for ALM. HER2 positive BC patients benefit from hormone therapy and/or antiHER2 or other targeted therapy.

The Ki-67 level is important for discrimination of LA and LB. As a prognostic factor, it is routinely studied for BC [5, 14]. Cheang et al. [2] identified that the ideal cut-off value of Ki-67 distinguishing LA and LB subtypes as 14%. It entered clinical use in 2011 St. Gallen International Expert Consensus on the Primary Therapy of Early BC [15]. In the study of Jin et al. [16], they concluded that Topo II α and Ki-67 expression were well correlated with the number of metastatic lymph nodes. So, that the positive expression of Ki-67 in BC tissues can be regarded as a determinant for prognosis. Costa et al. [17] claimed that Topo II α and Ki-67 together were beneficial to the prognosis determination of BC and postoperative therapeutic regimen is well selected, and Topo II α and Ki-67 together predict chemotherapeutic efficacy. In the present study, Ki-67 index was found significantly affecting ALM.

As the limitation of the study, some data was missing, such as number of excluded cases and radiologic imaging modalities' reports other than ultrasonography/ mammography.

In conclusion, HER2 positivity, Ki-67 index, and progesterone receptor negativity affect ALM significantly. HER2 and Ki-67 as prognostic markers may play an important role in the choice of treatment and may give survival benefits.

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