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RESEARCH

CORRELATIONS OF HISTOPATHOLOGICAL FEATURES WITH AXILLARY LYMPH NODE INVASION AMONG PATIENTS WITH BREAST CANCER IN GERIATRIC AND NON-GERIATRIC POPULATIONS

ABSTRACT

Introduction: In this study, it was aimed to investigate the relationships between immunohistochemical parameters and axillary lymph node metastasis in female patients with breast cancer. Additionally, age related differences between patient groups were investigated.

Materials and Method: Medical records of patients who underwent surgery for breast cancer during the last ten years were evaluated. The patients were divided into two groups according to their age: above group 1and below group 2, 65 years. Patient age, tumor stage, estrogenic and progesterone receptor status, C-erbB-2 oncogene and p53 tumor suppressor gene status and axillary lymph node status were recorded and analyzed for both groups.

Results: There were 43 patients with a mean age of 72 in G1 and 148 patients with a mean age of 48 in G2. We detected a positive correlation between axillary lymph node metastasis and p53 mutation for all patients, and this correlation was statistically significant in G2 ($p<0.001$). Different correlations however not statistically significant were observed between the other immunohistochemical parameters and axillary lymph node metastasis.

Conclusion: Immunohistochemical parameters, particularly p53 mutation, may indicate axillary lymph node metastasis and tumor prognosis in patients with breast cancer.

Key Words: Breast Neoplasms; Geriatrics; Pathology; Lymphatic Metastasis.

ARAŞTIRMA

MEME KANSERLİ YAŞLI VE GENÇ HASTALARDA HİSTOPATOLOJİK ÖZELLİKLER VE BUNLARIN KOLTUK ALTI LENF BEZİ TUTULUMU İLE İLİŞKİSİ

ÖZ

Giriş: Bu çalışmada, meme kanserli hastalarda immunhistokimyasal parametreler ile aksiller lenf nodu metastazı arasındaki ilişkinin araştırılması amaçlanmıştır. Aynı zamanda hasta grupları arasında yaşa bağlı olabilecek farklılıkları da araştırılmıştır.

Gereç ve Yöntem: Son 10 yıl içinde meme kanseri nedeniyle ameliyat edilen hastalara ait dosyalar incelendi. Hastalar 65 yaş ve üstünde olanlar grup 1ile 65 yaşın altında olanlar grup 2 şeklinde iki gruba ayrıldı. Hasta yaşı, cinsiyeti, tümör evresi, östrojen ve progesteron reseptör durumu, C-erbB-2 onkogen ve p53 tümör baskılayıcı gen durumu, aksiller lenf nodu tutulumu her iki grup için de kayıt edilip değerlendirildi.

Bulgular: G1 de yaş ortalaması 72 olan 43 hasta, G2 de ise yaş ortalaması 48 olan 148 hasta vardı. Aksiller lenf nodu metastazı ile p53 mutasyonu arasında tüm hastalar için pozitif bir korelasyon saptadık ve bu korelasyon G2 için istatistiksel olarak anlamlı idi ($p<0.001$). Diğer immunhistokimyasal parametreler ile aksiller lenf nodu durumu arasında istatistiksel olarak anlamlı olmayan farklı korelasyonlar vardı.

Sonuç: İmmunhistokimyasal parametreler ve özellikle p53 mutasyonu meme kanserli hastalarda aksiller lenf nodu metastazı ve dolayısı ile de tümör prognozunda belirleyici olabilir.

Anahtar Sözcükler: Meme Kanseri; Geriatri; Patoloji; Lenfatik Metastaz.

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Introduction

Excluding skin cancers, breast cancer is the most common cancer diagnosed among women, accounting for nearly one-third of all female. Breast cancer is also the second leading cause of cancer death among women after lung cancer (1). The incidence of breast cancer has also increased in Turkey, and the estimated number of breast cancer cases was 44,253 in 2007 (2). According the statistical data of Ministry of Health breast cancer was the most common type of female cancer in the first 10 ranks with 40.6 percentages in 2009 (3). Breast cancer risk increases with increasing age (1,2). The lifetime risk for breast cancer has increased due to a longer life expectancy. In the United States, nearly 99,220 new invasive breast cancer cases were reported in patients 65 years and older in 2013. This number corresponded to 42.7 percent of breast cancer for all age groups (1). In this study, we aimed to compare estrogene (ER) and progesterone receptor (PR) status, C-erbB-2 oncogene positivity, p53 tumor suppressor gene status and axillary lymph node (ALN) invasion degree in geriatric and non-geriatric patient groups.

Materials and Method

Participants and Study Design

After the approval of the local institution's ethics committee, a retrospective study was designed based on the hospital database. The files of patients who were diagnosed with breast cancer between January 2005 and January 2014 were scanned. These patients had been diagnosed preoperatively via needle, incisional or excisional biopsy, or had undergone surgery for an unknown breast mass and were diagnosed by frozen section. None of the patients had received neoadjuvant therapy. The surgical procedure for all patients was modified radical mastectomy (MRM), and histopathological records of the mastectomy and axillary dissection materials were investigated. Initially, 213 patient files obtained from one training and research hospital, one state hospital and one private hospital were reviewed, 22 patients were excluded due to missing data in the files, male gender, treatment with neoadjuvant therapy or alternative surgical procedure. Thus, 191 patients were included in the study. Patients for whom age, gender, stage according to the TNM scoring system (i.e., T: Tumor, N: Lymph node or M: Metastasis, according to the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), (7th Edition)), and ER, PR, C-erbB-2 oncogene and p53 tumor suppressor gene status were available were enrolled in the study. Immunohistopathological findings were compared with axillary lymph node status. All patients were female. The patients were divided into two groups according to age: 65 years or above (i.e., G1: group 1 or geriatric group) and below 65 years (i.e., G2: group 2 or non-geriatric group).

Statistical Analysis

Data analysis was performed using SPSS 22 for Windows (Chicago, IL, USA). The Levene test was used to evaluate homogeneity of variances. The data were presented as mean ± standard deviation or median (min–max), where applicable. Differences between groups were compared using Student's t-test or the Mann–Whitney U test, where appropriate. Categorical data were analyzed using the Pearson chi-square test, where appropriate. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 191 patients were included in the study, with a median age of 51 (27-88) years. Forty-three (22.5%) patients were included in G1, and 148 (77.5%) patients were included in G2. All patients had undergone MRM surgery. Tumors were located in the right breast in 103 cases and in the left breast in 88 cases. Infiltrative ductal carcinoma was the unique histopathological cancer type in all cases. According to the histopathological TNM staging system, the majority of patients were in stage 2a (51 cases, 26.7%). Each of 102 patients had at least one ALN metastasis (N1). These findings are summarized in Table 1 and Table 2. The results of

Table 1— Histopathological Details for All Patients.

		n (%)
Histopathological Stage (TNM)*	DCIS**	3 (1.6)
	Stage 1	50 (26.2)
	Stage 2a	51 (26.7)
	Stage 2b	42 (22.0)
	Stage 3a	29(15.2)
	Stage 3b	4 (2.1)
	Stage 3c	11 (5.8)
	Stage 4	1 (0.4)
Lymph Node Metastasis*	N0	89 (46.6)
	N1	102 (53.4)

*T: Tumour N: Lymph node M: Metastasis According to Union for International Cancer Control - UICC and American Joint Committee on Cancer - AJCC , 7th Edition

**Ductal carcinoma in situ.

Table 2— The Between-Groups Comparisons of Demographic Characteristics and Lymph Node Status.

	Group 1	Group 2	Total
Patient number	43	148	191
Mean age (year)	71.9±5.6	47.4±8.6	52.9±13.0
Lymph node metastasis	25	77	102

Group 1: Geriatric population, Group 2: Non-geriatric population.

immunohistochemical staining for ER, PR, C-erbB-2 and p53 status were compared to histopathological ALN metastasis. No significant relationship was observed between the immunohistochemical parameters and ALN metastasis in the geriatric patient group. A significant positive relationship was observed between p53 mutation and ALN invasion in the non-geriatric group ($p<0.001$) (Table 3). An analysis of the correlations between the number of metastatic ALNs and the immunohistochemical parameters revealed different results in the two groups. In G1, negative correlations existed between C-erbB-2 and ALN invasion and between PR positivity and ALN invasion. However, in the same group, positive correlations were observed between p53 mutation and ALN invasion and ER positivity and ALN invasion. However, in the same group, positive correlations were observed between p53 mutation and ALN invasion and ER positivity and ALN invasion. In contrast, in G2, negative correlations were observed between ER and PR positivity and ALN invasion. However, in the same group, positive correlations were observed between C-erbB-2 positivity and ALN invasion and p53 mutation and ALN invasion. These correlations were not statistically significant, except for the correlation of p53 with ALN metastasis in G2 and in the total patient population (Table 4).

Discussion

Breast cancer remains an important health problem despite improved diagnosis and treatment. The proportion of elderly people in the general population has increased due to longer life expectancy and lower birth rates. ALN metastasis is one of the most important prognostic factors in patients with breast cancer, and higher mortality rates correspond to increased axillary invasion (4, 5). Geriatric breast cancer differs from non-geriatric breast cancer, and researchers have recently focused on these points (6). We aimed to investigate the relationships between immunohistochemical parameters

Table 3— Immunohistochemical Parameters and Their Relation to Axillary Lymph Node Metastasis.

	Group 1			Group 2			Group 1+2		
	No	N1	p value	No	N1	p value	No	N1	p value
C-erbB-2	9/17	12/24	0.855	35/69	46/76	0.237	44/86	58/100	0.351
ER	14/18	15/23	0.386	49/70	47/75	0.353	63/88	62/98	0.228
PR	13/17	14/25	0.179	45/68	41/72	0.264	58/85	55/97	0.111
P53	5/17	10/24	0.428	9/59	38/75	**<0.001**	14/76	48/99	**<0.001**

Group 1: Geriatric population, Group 2: Non-geriatric population, Group 1+2: All patients.
ER: Estrogen receptor, PR: Progesterone receptor.

Table 4— Correlations Between Axillary Lymph Node Metastasis and Immunohistochemical Parameters By Group.

Immunohistochemical parameter – The number of axillary lymph node metastases	Group 1		Group 2		Group 1+2	
	Corr.	p	Corr.	p	Corr.	p
CerbB-2	- 0.098	0.541	+ 0.112	0.179	+ 0.064	0.383
ER	+ 0.017	0.918	- 0.109	0.191	- 0.077	0.297
PR	- 0.105	0.510	- 0.116	0.172	- 0.110	0.141
P53	+ 0.146	0.361	+ 0.314	<0.001	+ 0.273	<0.001

Group 1: Geriatric population, Group 2: Non geriatric population, Group 1+2: All patients.
ER: Estrogen receptor, PR: Progesterone receptor.

and ALN metastasis and identify differences between patients aged over 65 and patients under age 65.

ER and PR measurements are essential prior to treatment because the presence of these proteins indicates that the patient will benefit from hormone therapy (7). Elderly patients with breast cancer exhibit increased expression of ER and PR, and hormone therapy is advocated as the primary therapy for this population (8-10). Our geriatric patients exhibited 71.4% ER positivity and 65.1% PR positivity, while non-geriatric patients exhibited 66.0% ER positivity and 61.1% PR positivity. A positive correlation was observed between ER and ALN metastasis (p = 0.918) in the geriatric patient group, but a negative correlation was observed between these parameters in the non-geriatric group (p = 0.191). We observed negative correlations between PR and ALN metastasis in both groups (the associated p values were 0.510 and 0.110, respectively). These findings were not statistically significant. Mutlu et al. found no differences in receptor status between 108 geriatric and 183 non-geriatric patients with breast cancer (6).

C-erbB-2 is an oncogene for which increased expression indicates a poor prognosis and a higher probability of recurrence among patients with breast cancer (7, 11, 12). We detected positivity for C-erbB-2 in 52.4% of G1 and 55.6% of G2. Over expression of human epidermal growth factor occurs in approximately 20-25 % of invasive breast cancers (13). A comparison of correlations between C-erbB-2 and ALN metastasis revealed a negative correlation in geriatric patients (p = 0.541) and a positive correlation in non-geriatric patients (p = 0.179); however, these correlations were not statistically significant. Slamon et al. (14) reported that 40% of ALN-positive breast cancer patients exhibited C-erbB-2 expression, with a 2- to 7-year follow up.

P53 is a tumor suppressor gene that is activated to eliminate DNA damage caused by ultraviolet light and other carcinogens. If the damage fails to be repaired, the cell is directed to undergo apoptosis. Close relationship was observed between a damaged chromosome 17, which carries the p53 gene, and histopathological characteristics of breast cancer (15, 16). Excessive production of mutant p53 in tissues is an indicator of poor prognosis in breast cancer patients. We detected positivity for mutant p53 in 35.7% of G1 and 34.6% of G2. Sirvent et al. (16) reported 45.3% positivity for p53 in an immunohistochemical analysis of 192 cases of infiltrating ductal carcinoma of the breast and concluded that a prognostically significant relationship exists between the expression of p53 and shorter survival time and disease-free interval. This is relevant for all patients as well as for those who presented with lymph-node metastases at the time of diagnosis. Our findings demonstrated that a positive correlation existed between high p53 mutations and ALN metastasis in each group; this correlation was statistically significant in the non-geriatric group and in the total patient population (the associated p values were 0.361, <0.001 and <0.001 for G1, G2 and G1+G2, respectively).

In conclusion, immunohistochemical parameters in breast cancer patients may predict prognosis. Higher p53 mutations indicate increased ALN metastasis. Particularly in the non-geriatric patient population, these findings are critical and indicate a poor prognosis.

Conflict of Interest

None

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