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Retrospective Evaluation of the Female Patients with Breast Cancer: Western Black Sea Region, Unicentered, Clinical Data of Oncology

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ABSTRAC

Breast cancer is the most common female cancer in the world wide with 30% of all women cancer and second most common cause of cancer death in women. Oncology department of Bulent Ecevit University Faculty of Medicine is the only cancer center in western part of Black Sea region. We investigated retrospectively our data of women breast cancer between the period of 2000 and 2010 in this region. The mean age of the study population was 49.90 ± 12 years and mean follow-up time was 4 ± 2 years. The distribution of patients by the age, 25% or patients under 40 years old, 32% between the 40-50 years old and 43% of them over the 50 years old. 92.6% of the patients were presented with a palpable mass. The most common type of breast cancer was invasive ductal carcinoma (IDC) in 312 patients (80%). Prognosis of the study population; 309 patients (80%) are surviving without any disease. Sixty-six patients (17%) had progression, 7 of 390 patients (1,8%) had local recurrence and 15 patients (3.8%) died. While the breast cancer is one of the most commonly seen solid organ tumors in Black Sea region and, based on the literature, no significant differences were observed for prognostic factors, longer life expectancy of the patients with advanced stage disease may be attributed to higher number of patients with hormonal positivity and therapy adherence.

Keywords: Breast cancer, Woman, Prognosis, Survival

ÖZET

Meme Kanserli Kadınların Retrospektif Analizi: Batı Karadeniz Bölgesi Tek Merkez Onkoloji Klinik Verileri

Meme kanseri tüm dünyada kadınlardaki en sık kanser türü olup kadın kanserlerinin %30'nu oluşturur ve kadınlarda kansere bağlı en sık ölüm nedenidir. Bulen Ecevit Üniversitesi Onkoloji Bölümü Batı Karadenizdeki tek kanser merkezidir. 2000 ila 2010 yılları arasında kadınlarda meme kanserini retrospektif olarak araştırdık. Çalışmamızdaki populasyonun ortalam yaşı 49.90 ± 12 'di ve ortalama takip süresi 4 ± 2 yıldı.Hastaların yaşa göre dağılımında %25'ini 40 yaş ve altı, %32'sini 40-50 yaş arası oluşturmaktayken kalan %43'de 50 yaş ve üzeri hastalar oluşturmaktaydı.En sık görülen kanser tipi 312 hastada saptanan invazif duktal karsinomdu (%80). Hastaların prognozuna baktığımızda; 309 hasta(%80) hastalıksız sağkalımda, 66 hastada (%17) progresyon, 7 hastada (%1,8) local nüks ve 15 hastada (%3,8) ölüm görüldü. Meme kanseri Batı Karadeniz bölgesindeki kadınlarda en sık görülen solid organ tümörlerden olup prognostik faktörler ve ileri evre hastalığı olanlardada uzun yaşam beklentisi açısından anlamlı bir fark saptanmadı. Hormonal pozitiflik ve tedavi uyumu bu duruma en önemli katkıyı sağlamaktaydı.

Anahtar Kelimeler: Meme kanseri, Kadın, Prognoz, Sağkalım

INTRODUCTION

In the epidemiological studies conducted, breast cancer accounted for 28-32% of all the cancers and for 17.6% of the cancer-related deaths among women worldwide.[1,2] One out of 9 women have the risk for the development of invasive breast cancer in their life time.[3]

In our country, based on the data published by Ministry of Health, in 2005, a total of 24815 patients were diagnosed with cancer and the incidence of cancer was calculated as 173.85 in 100,000. Of all cases of cancer, 4466 were the patients with breast cancer, which was the most common type of cancer with a percentage of 35.47%.[4] Furthermore, in an epidemiological study performed by Fidaner et al. in the region of Izmir, the incidence of breast cancer was found to be 23.4/100.000 in this region.[5]

Lymph node status and the size of the tumor are the most important prognostic factors in terms of the recurrence of breast cancer and overall survival.[6,7] Other prognostic factors include the grade of the tumor, lymphatic and vascular invasion, Ki-67 proliferation marker, the age of the patient at the time of diagnosis, estrogen and progesteron receptor status, Human Epidermal Growth Factor Receptor 2 (HER-2/neu) status, urokinase plasminogen activator (uPA) and plasminogen activator inhibitor-1 (PAI-1) genetic profile.[8]

In this study, we aimed to investigate the statistical information, early diagnosis and prognostic factors, by retrospectively evaluating the clinical and laboratory data of the patients with breast cancer, who were admitted to and then followed up in Bulent Ecevit University, Clinical Practice and Research Hospital, Medical Oncology outpatient clinic between 2000 and 2010.

MATERIAL AND METHODS

In this study, the clinical and laboratory data of the patients with breast cancer, who were admitted to and followed up in Bulent Ecevit University, Practice and Research Hospital, Medical Oncology outpatient clinic between 2000 and 2010, were retrospectively evaluated. During that period, among 470 patients, records of 390 patients which were available were retrospectively evaluated. The following information were recorded for each of the subjects: age, complaints at the time of presentation, familial history, tumor localization, the type of surgery performed, pathological TNM classification, histopathological type of the tumor, the grade of the tumor, estrogen, progesteron and cerb2 receptors status, the number of the lymph nodes involved, adjuvant therapies received, status of metastasis, the sites of metastasis, metastasis at the time of diagnosis, and the rates of death or disease-free survival. Based on this information, each patient was staged using TNM staging system based on American Joint Committee clinical staging system 2003 (AJCC).

Duration of follow-up was considered as the time from the diagnosis to the end of the study. A disease-free survivor group was formed by excluding the patients with progression and death from overall cases. The patients, who were controlled at least 3 months ago, were contacted via telephone and their data were updated by February 2010. Finally, the actual statuses of disease-free survival, progression or exitus of the patients were demonstrated.

Statistical Analysis: In the analysis of the study, SPSS 18.0 software was used. Descriptive statistics were reported as the mean or median with standard deviation. Unpaired t tests were performed for data with normal distribution. For parameters that did not show normal distribution, the non-parametric Mann Whitney U test was used to compare. Between-group analyses were performed using one-way ANOVA or chi-squrae. Kaplan-Meier and Cox regression analysis were used in the analysis of time to event variable and the 95% confidence interval (CI) for the median time to event was computed. The 95% CI was selected, and p value of 0.05 was set for statistically significance. Correlations were studied using Spearman correlation coefficient.

RESULTS

The study was performed on 390 subjects who were admitted to, treated and followed up at Bulent Ecevit University, Practice and Research Hospital, Medical Oncology Outpatient Clinic between 22.10.2000 – 01.01.2010. The age distribution of these patients was as follows, 24.7% were ≤40 years-old, 31.5% were between 40-50 years-old and 43.8% were ≥50 years-old. Mean age of the patients was 49.90±12 years. The total person time of

Table 1. The histopathological distribution of the patients

	Number	%
IDC	312	80.0
ILC	26	6.7
IDC+ILC	12	3.1
Mucinous	10	2.6
Medullar	8	2.1
DCIS	7	1.8
Tubular	4	1.0
Ppillar	3	0.8
Mesenchymal Tumor	3	0.8
LCIS	2	0.5
IDC+DCIS	2	0.5
IDC+DCIS+LCIS	1	0.3
Total	390	100.0

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, DCIS: Ductal carcinoma insitu, LCIS: Lobular carcinoma insitu

Table 2. Five years survival rates according to hormonal status

	Patients	Cummulative 5 years survivall (%)
ER negative	101	89
ER +	102	96
ER++	79	97
ER+++	75	95
ER++++	33	100
PR negative	120	92
PR positive	270	97
CerbB2 negative	335	95
CerbB2 Positive	55	89

ER: Estrogen receptor, PR: Progesterone receptor, CerbB2: Human Epidermal Growth Factor Receptor 2

follow-up was 1703 years. The median follow up time was 5 (1-10) years. The most common complaint at the time of presentation was a palpable mass, with a rate of 92.6%. Of the patients, 3 (0.8%) had nipple discharge, 12 (3.1%) had pain + nipple discharge, 4 (1%) had redness, 4 (1%) had only pain and 6 of the patients (1.5%) were detected during the examination. When the tumor localization was evaluated in the cases, 200 patients (51.3%) had a tumor localized in the right breast, 183 patients (46.9%) had a tumor localized in the left breast, and 7 patients (1.8%) had a tumor localized in both breasts. The pathologic subtypes of breast cancer were presented in the Table 1.

There is a significant correlation between the metastatic lymph node number and overall survival (Pearson correlation coefficient = 0.65; p= 0.037). There is a negative correlation with cerbB2 status and overall survivals (OS) (p= 0.0001). According to the immunohistochemical analysis, CerbB2 negative, one and two positive values accepted negative hormonal status because these patients didn't recieved trastuzumab treatment. CerbB2 3+ and 4+ accepted positive and treated with trastuzumab. There is no statically significant differences of OS between the positive/negative cebrB2 status (p= 0.19). When the survival rates were evaluated according to the stages, 5 years survivall rate was 98% and 10 years survivall rate was 94%. According the ER, PR and CerbB2 status, relationships between the each categorical variable with OS measured by chi-square test. For ER status there was no significant difference between the quantity of ER positivity with OS (p= 0.052) and also there was significant difference between the PR negative and PR positive patients for OS (p= 0.21). CerbB2 status did not effect the survival (p= 0.19) and these parameters presented in the Table 2. Of 101 patients (25.9%) that were ER-negative, 6 died. Of 120 patients (30.8%) that were PR-negative, 5 (33.3%) died.

At the time of diagnosis of breast cancer, menopause status was presented in Table 3. Of the cases investigated, 334 patients (85.6%) underwent modified radical mastectomy (MRM) as the surgical therapy. Two patients (0.5%) underwent radical mastectomy (RM), 20 patients (5.1%) underwent lumpectomy + ad and 32 (8.2%) underwent simple mastectomy. Two patients (0.5%) were considered as inoperative.

Table 3. Menopausal status at the time of diagnosis of breast cancer

	Number	%
Pre-menopausal	156	40
Peri-menopausal	60	15.4
Post-menopausal	174	44.6
Total	390	100.0

Stage is one of the most important prognostic factor. With advanced stage, the rate of survival decreases. 5 years OS was 97% in the early stage but 74% in the stage 4 (p= 0.0001) also had shown in Figure 1.

Of 390 patients examined, 7 (1.8%) had local recurrence, 81 (20.8%) had metastasis, 15 (3.8%) died. When the sites of metastasis were evaluated, bone was the most common site of metastasis with 33 patients (40.7%). When, together with bone metastasis, liver, lung and brain metastasis were calculated, 54 patients (66.5%) showed bone metastasis. This was respectively followed by liver metastasis in 8 patients (9.9%), lung metastasis in 8 patients (9.9%), bone + liver metastasis in 7 patients (8.6%), bone + brain metastasis in 7 patients (8.6%), skin metastasis in 6 patients (7.4%), and bone + liver + lung metastasis in 4 patients (4.9%).

Three hundred fourty-one patients (87.4%) received adjuvant chemotherapy. Forty-nine patients (12.6%) could not receive chemotherapy. When the chemotherapy regimens were evaluated, the most commonly administered regimen was AC (doxorubicine + cyclophosphamide) with 185 patients (47.4%) and their survival rate was 95.6%. Second most commonly administered chemotherapy regimen was FEC (5-fluorouracyl + epirubicine + cyclophosphamide) which was given to 75 patients (19.2%) and the survival rate of these patients was 98.6%. Third most commonly administered chemotherapy regimen was CAF (5 fluorouracyl + doxorubicine + cyclophosphamide) that was given to 57 patients (14.5%) and the survival rate of these patients was 94.7%.

It was found that, of the patients enrolled to the study, 309 (79.2%) were disease-free survivors, 66 (17%) showed progression and 15 (3.8%) died.

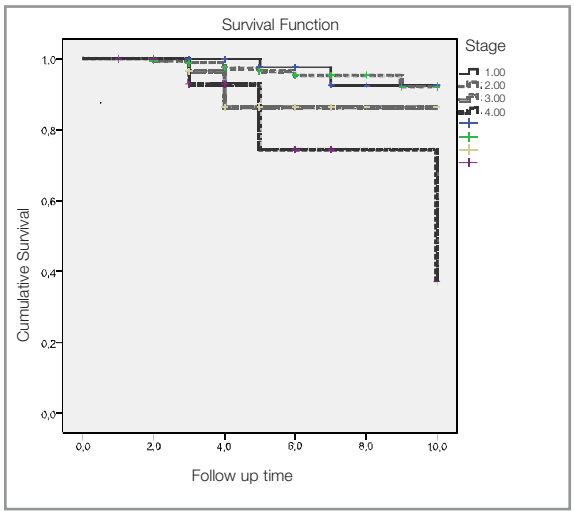

Figure 1. Overall Survival for Stage of Breast cancer

DISCUSSION

Based on the data from our clinic, which is the only oncology center in the Black Sea region, we concluded that age is an important independent risk factor for breast cancer. In our study, we found that "palpable mass" was the first detected finding in the breast cancer, and in the presence of perineural invasion, the involvement of lymph node was higher, and with the increasing number of axillar lymph nodes involved the survival rates remained stable and in our region, ER-positive and PR-positive breast cancers were more common compared to the data in the literature (respectively, 74.2% and 69.2%). We found that 87.4% of our patients received adjuvant chemotherapy and that disease-free survival rate of our patients was 79.2%.

The idea that the breast cancer is not only a disease but it should be considered as a combination of different pathological processes, with different courses and prognosis is increasingly accepted. Long-term survival is not primarily and solely determined with early diagnosis, but is also based on the biological behavior and the malignancy potential of the tumor.[9]

The breast cancer incidence shows a marked increase with advanced age. When we examine the age distribution of 390 patients enrolled to our study, we observed that mean age was 49.90±12 years and 75.3% of the patients were ≥40 years-old. This finding overlaps with the reality that the age is an im-

portant independent risk factor for the breast cancer. In a study performed on 1381 subjects, the number of the patient with breast cancer in the 40-70 years of age group was 67.5% of all the subjects.[10]

When we examine the complaints of our patients during admission, we see that the most common reason of presentation is "palpable mass" (92.6%). In the literature, it is highlighted that 70% of the women with breast cancer presents with a mass in the breast as the first finding.[11,12]

Involvement of axillar lymph nodes is an important prognostic factor for the breast cancer. The status of the axillar lymph nodes leads better selection of the patients that require adjuvant chemotherapy and local radiotherapy. In many clinical studies, although the patients were grouped as node (-), 1 -3 nodes (+) and > 4 nodes (+), a direct proportion was determined between the number of the nodes involved and the clinical course.[13] In the study conducted by Nemoto et al.[14], it was found that while the axillar involvement increases, the survival rate decreases. In the study performed by Martin et al.[15], it was found that 8-year survival rate was 87.5% in the patients with no axillar involvement, 85.5% in the patients with 1 node involved and 49.1% in the patients with ≥2 lymph nodes involved, and that the impact of the axillar involvement on the survival rate was statistically significant. In our study, we also found significant negative correlation between the lymph node invasian with OS.

The stage of the tumor is an important indicator of the survival, alone and/or together with other prognostic factors. In our study, the most commonly seen stage of tumor was Stage 2A, with a rate of 40.3%. This resulted from the fact that the patients presented to the doctor in the late stage and when they were symptomatic. When we compared our data with other data of the literature, the survival rates of our patients with Stage 1 and Stage 2 were consistent with others, but, the survival rates of our patients with Stage 3 and Stage 4 were higher in our population. Given that our median duration of follow-up was 5 years, our results corresponded to the results obtained in the literature. One reason of these high values could be the hormonal status as ER and PR are independent prognostic factors in the breast cancer. ER and PR positivity indicates the response to hormonal therapy and a better prognosis. On average 55-65% of the cases with primary breast cancer are ER-positive. Approximately 45-60% of the cases with breast cancer are PR-positive. In our study, ER and PR positivity was found to be respectively 74.2% and 69.2% and this could explain the contribution to the survival.

Although it is generally highlighted that there is a relation between the decrease of survival and Cerb-B2 positivity, it should be noted that the results about the survival are conflicting. Paik et al.[16] found a correlation between Cerb-B2 positivity and the decreasing survival only in the patients that have a tumor with a good nuclear grade. Again, Slamon et al.[17] showed in their multivariate analysis that there was a significant independent correlation between Cerb-B2 positivity and the recurrence and poor survival. There are also some studies that indicate the relation between the decreased survival and Cerb-B2 positivity in the cases with Cerb-B2 positivity in their axillar area.[18] In our study, when we examine the survival rates according to stages, we see that, with advanced stage, the rate of death increases and the survival rate decreases. We also found a negative correlation between the cerbB2 status and OS but there is no statically significant.

During the last few years, observed decrease in the mortality of breast cancer was also due to the development of adjuvant therapies. Current guidelines recommend adjuvant chemotherapy following the systemic surgery. In a study, it was seen that polychemotherapy reduced post-operative recurrences and deaths in the patients below 70 years-old and with tamoxifen similar results achieved in all age groups.[19] Therefore, current guidelines recommend adjuvant chemotherapy for all patients, regardless of the age. We found that, of the patients that we screened, 87.4% had received adjuvant chemotherapy. We determined that the most commonly administered chemotherapy regimens were AC (doxorubicine + cyclophosphamide) with a rate of 47.4%, FEC (5-fluorouracyl + epirubicine + cyclophosphamide) with a rate of 19.2% and CAF (5 fluorouracyl + doxorubicine + cyclophosphamide) with a rate of 14.5%. For all of the 3 chemotherapy regimens, mean survival rate was 95%.

Radiotherapy has an important role in the adjuvant therapy administered for early breast cancer. In our

study, we found that 71% of the patients received radiotherapy. For the radiotherapy given after the surgical therapy for breast cancer, the effect on survival rate and the contribution to the prevention of the local and regional recurrences are clearly established.[20]

The histopathological classification accepted today is performed according to tumor characteristics and the source cells. Ninety percent of the breast tumors are consisted of invasive ductal carcinoma (IDC) + invasive lobular carcinoma (ILC).[21] Ductal breast cancers are 80% of all breast cancers. In our study, IDC + ILC were found to be 90.6%.

As the site of metastasis, we found that the most common metastasis were bone metastasis with a rate of 66.5%. This was respectively followed by liver, lungs and brain. In a study performed, consistent with the results of our study, the most common site of metastasis was bone with a rate of 63.2%.[22]

The survival time of the untreated patients at a same clinical stage of the disease varies between several months to several decades.[23] At the end of our study, when we examined the ultimate condition of the patients, we found that 79.2% were disease-free survivors, 17% had progression and 3.8% died.

Consequently, while the breast cancer is one of the most commonly seen solid organ tumors in Black Sea region and, based on the literature, no significant differences were observed for prognostic factors, longer life expectancy of the patients with advanced stage disease may be attributed to higher number of patients with hormonal positivity and therapy adherence.

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