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Oncology

Early Stage Breast Cancer: Prognostic Factors Affecting Local Recurrence and Systemic Metastasis

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Original Research Article

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Abstract: Breast cancer is the most common cancer type in women in the world. The causes of death in patients undergoing surgery are relapses and metastases. Known prognostic factors affecting recurrence in these patients are age, tumor size, number of axillary lymph nodes, disease grade, ER, PR, HER-2 expression, and lymphatic invasion presence. We aimed to find prognostic factors that determine recurrence, early-late recurrence and risk of local and distant metastases in our patients with breast cancer. The files of patients with breast cancer who were referred to Dicle University Medical Faculty Medical Oncology Department between 2001 and 2010 were reviewed retrospectively. The recurrent-metastasis group of patients with recurrence during trials was called the remission group of other patients. Molecular features such as age, sex, tumor histology, size, number of lymph nodes, presence of lymphovascular invasion, tumor grade, ER, PR, HER among these two groups, staging studies; the recurrence group was compared with the recurrence-metastasis group in terms of time characteristics such as surgical characteristics, duration of surgery-chemotherapy and surgery-radiotherapy. Factors determining recurrence of early (≤24 months) and later (> 24 months) recurrence, local (local, same axilla, bone) and distant (locally external) SPSS 22 program was used for statistical analysis. A P value of <0.05 was considered significant. A total of 802 patients were included in the study of 479 breast cancer patients. Median age was 47 (18-79) years. Of the patients, 136 were involved in the recurrence-metastasis group and 343 were in the remission group. Lymphovascular invasion (lymphovascular invasion frequency, recurrence rate, p <0,05), lymph node metastasis (p <0,05), lymph node metastasis (p <0.05), greyd (percentage of middle and high graded patients were higher in the recurrent group, p <0.05), inadequate staging (recurrence was more frequent in patients with missing staging, p <0,05) and duration between surgery and chemotherapy and chemotherapy interval> 1 month, recurrence was more frequent (p <0.05). The factors determining the recurrence in patients with breast cancer were tumor size, number of involved lymph nodes, lymphovascular invasion, grade, incomplete staging, and the time between surgery and chemotherapy was 1 month. The factors determining late recurrence were ER positivity and use of adjuvant hormonal therapy. Local recurrence was associated with inadequate staging and distant metastasis and a significant association between ≥10 lymph node involvement.

Keywords: Early stage breast cancer, Local recurrence, Systemic metastasis, Prognostic factors.

INTRODUCTION

Breast cancer is a major health problem for women worldwide. Eight of all women have breast cancer at some point in their lives. It is the most common cancer in women in the United States; is the second leading cause of cancer-related deaths. According to annual cancer statistics, 26% of new cancer cases are breast cancer; it is estimated that 15% of cancer-related deaths will be from breast cancer [1]. Screening mammography, adjuvant chemotherapy and hormonal therapy have reduced mortality in breast cancer [2].

The cause of death in patients with breast cancer is relapses and metastases. The known prognostic factors affecting recurrence and metastasis in patients with breast cancer are listed as age of the patient, size of the tumor, number of axillary lymph node involvement, disease grade, tumor estrogen and

progesterone expression, Her-2 neu expression, and peritumoral lymphatic invasion presence.

In our study, we aimed to find prognostic factors affecting local recurrence, early and late recurrence evaluation, local and distant metastasis in patients receiving adjuvant treatment with breast cancer.

MATERIALS METHODS

A retrospective study of 802 breast cancer patients referred to the Department of Medical Oncology at the Dicle University Medical Faculty between 2001 and 2010 was reviewed. Patients who were metastatic at the time of diagnosis were excluded from the study. Patients who were operated on were included in the study. The recurrent-metastasis group of patients with recurrence during trials was called the remission group of other patients. Molecular features such as age, sex, tumor histology, tumor size, number of lymph nodes, presence of lymph node invasion, tumor grading, ER, PR, HER, chest X-ray, abdominal usg, scintigraphy and tomography are among these two groups; time characteristics such as surgical characteristics such as operative procedure, duration between surgery and chemotherapy and surgery-radiotherapy; the recurrent-metastasis group and the remission group were compared. Patients who subsequently developed recurrence were divided into two groups: early (≤24 months) and late recurrence (> 24 months). These two subgroups were compared in order to find the factors determining early and late relapse among these patients.

Patients with recurrence were divided into local (local, axilla, bone) recurrence group according to metastasis sites and distant metastasis (all recurrence sites except local recurrence sites). These two new subgroups were compared to find the determinants of metastasis location.

Informed consent was obtained from all patients for data use. The study was conducted following the guidelines of the Declaration of Helsinki.

STATISTICAL ANALYSIS

For the statistical analysis, SPSS (Statistical Package for Social Sciences) 22 program was used. Chi-square test, Fisher's Exact Chi-square test and student 't' test were used to compare descriptive statistics (mean, standard deviation) as well as qualitative data. the significance test of the difference between the two percentages was used. The results were evaluated in a confidence interval of 95% and a significance level of $p < 0.05$.

RESULTS

A total of 802 patients with breast cancer were examined retrospectively. Patients who were metastatic at the time of diagnosis were excluded from the study. 479 patients were included in the study. Patients who developed local recurrence and / or metastasis during the trial were included in the recurrence-metastasis group. In the remission group of 343 (72%) patients; 136 (28%) were in the recurrence-metastasis group. These two groups are age, gender, histology, number of lymph nodes involved, lymphovascular invasion, tumor grading, ER, PR, HER, operation type, chemotherapy regimen, chemotherapy toxicity, duration between surgery and chemotherapy, duration between surgery and radiotherapy, adjuvant hormonal therapy, staging studies, breast localization, disease-free survival and overall survival.

There was no statistically significant difference between the two groups (p> 0,005) in the remission group with a mean age of 48.7 years (median 47.0) (18-79) and in the recurrence-metastasis group a mean age of 47.9 years (median 45.0) .

Histological subgroup analysis remission group showed that ductal 276(81.2%), lobular 39 (11.5%), medullary 14 (4.1%), other 11 (3,2%) histological types. Of the 134 patients evaluated in the recurrent-metastases group, 117 (87.3%) were ductal 5 lobuler(3,7%), 8 medullar (6,0%), 4 other(3,0%) histological type.

Tumor diameter was 3.33 cm (median 3 cm) in the remission group and 4.58 cm (median 4 cm) in the recurrence-metastasis group and there was a statistically significant difference between the two groups ($P < 0.001$). The tumor diameter in the majority of patients was T2 (2-5 cm). There were 234 (73.8%) in the remission group and 83 (26.2%) in the recurrent metastasis group.

Significant significance was found for the number of lymph nodes involvement ($P < 0.001$). There was a greater number of lymph node involvement in the recurrent-metastases group. There was a significant difference in lymphovascular invasion ($P < 0.001$). Lymphovascular invasion in the recurrent metastases group was more prominent.

There was a significant difference between the two groups in terms of tumor grade ($P = 0.021$). Tumor grade was more advanced in recurrent metastases group.

There was a significant difference between the two groups in terms of tumor diameter ($P < 0.001$). Tumor diameter was larger in recurrent-metastasis group ($p < 0.001$).

There was no statistically significant difference between the two groups regarding ER, PR, HER.

When patients were analyzed in terms of the type of operation, 90.2% of the patients who developed recurrent metastases showed MRM operation.

When the patients were evaluated in terms of treatment duration and recurrence relation; In the remission group, 90.3% (n = 298) and 9.4% (n = 32) patients with 0-1 month survival were found to be between surgery and chemotherapy. In the recurrent-metastasis group, the percentage of patients 0-1 months was 76% (n = 95) and > 1 month 24% (n = 30). Statistically significant differences were found between the two groups (p <0.001).

When evaluated in terms of other features, patients were more likely to have recurrence than those who did not receive it in the radiotherapy field.

It was statistically significant that recurrence was more frequent in patients with missing staging at the time of diagnosis (p <0,001) 30.9% in the remission group; 47.7% of the patients in the recurrence-metastasis group were incomplete at the time of diagnosis.

There was no statistically significant difference between pathologic features and early and late recurrence in terms of histology, number of involved lymph nodes, lymphovascular invasion, tumor diameter, grade, PR, HER. There was statistically significant correlation between ER positivity and late recurrence (p = 0,031)

Table-1: Patient characteristics

		Groups		Total	P value
		Remission-(%)	Recurrence-met (%)		
Age	Age(year) < 40	84-(%24,5)	33-(%24,3)	117	0,189
	Age(year) 40-70	247-(%72)	93-(%68,4)	340	
	Age(year) >70	12-(%3,5)	10-(%7,4)	22	
	Total	343(%72)	136(%28)	479	
Sex	Female	341-(%99,4)	133-(97,8)	474	0,115
	Male	2-(%0,6)	3-(%2,2)	5	
	Total	343	136	479	
Histology	Ductal	276-(%81,2)	117-(%87,3)	393	0,061
	Lobular	39-(%11,5)	5-(%3,7)	44	
	Medullar	14-(%4,1)	8-(%6,0)	22	
	Other	11-(%3,2)	4-(%3,0)	15	
	Total	340	134	474	
Lymph Node	N0	131-(%39,1)	18-(%14)	149	<0,001
	N1 (1-3)	102-(%30,4)	39-(%30,2)	141	
	N2 (4-9)	63-(18,8)	46-(%35,7)	109	
	N3 (>10)	39-(%11,6)	26-(%20,2)	65	
	Total	335	129	464	
Lymphovascular invasion	Unknown	132-(%72,5)	50-(%27,5)	182	<0,001
	Positive	96-(%46,4)	68-(%80)	164	
	Negative	111-(%53,6)	17-(%20)	128	
	Total	339	135	474	
Grade	Grade 1 (good)	29-(%12,0)	3-(%2,8)	32	0,021
	Grade 2 (moderate)	132-(%54,5)	66-(%60,6)	198	
	Grade 3 (bad)	81-(%33,5)	40-(%36,7)	121	
	Unknown	99-(%79,8)	25-(%20,2)	124	
	Total	341	134	475	
Tumor diameter	Tx	22-(%6,4)	6-(%4,4)	28	<0,001
	<2 cm T1	45-(%13,2)	5-(%3,7)	50	
	2-5 cm T2	234-(%68,4)	83-(%61,5)	317	
	>5 cm T3	26-(%7,6)	36-(%26,7)	62	
	T4	15-(%4,4)	5-(%3,7)	20	
	Total	342	135	474	

DISCUSSION

Breast cancer is the main health problem for women in our country and in the world. The most common cancer observed in women in our country is breast cancer. Mortality in breast cancer is associated with local recurrence and distant metastasis. Due to increased screening, most patients are confronted at an early stage. Adjuvant chemotherapy and hormonal

therapy reduce recurrence and mortality in breast cancer [3]. Adjuvant is the goal of systemic treatment to eradicate asymptomatic micrometastatic disease. Most of the patients benefit from adjuvant systemic treatment. Prognostic factors that may determine the risk of micrometastatic disease are needed at the time of diagnosis so that patients can benefit maximal benefit from treatment. Tumor size, lymph node involvement grade, ER, PR, Her-2 / neu, lymphovascular invasion presence are known prognostic factors [4]. The larger the primary tumor in breast cancer, the worse the prognosis. There is an accurate ratio between tumor size and recurrence and distant metastasis,independent of the node involvemnt. In a study that did not show a relationship between 20-year tumor size and recurrence-metastasis survival, Rosen et al. found that the duration of disease-free survival shortened as tumor size increased [5]. The 5-year survival rate of the tumors smaller than two centimeters is the highest. Carter and colleagues found that tumor size was an independent prognostic factor for survival in the study of 24,740 breast cancer patients. The 5-year survival rate was 96.3% in patients with tumor size less than 2 cm; In patients with a tumor size of 5 cm and over, this rate was 45.5%. In retrospective prognostic index determination study performed by Galea et al. In 387 breast cancer patients, tumor size was found to be a prognostic factor. In our study, mean tumor diameter remission was 3.33 cm (median 3 cm) in the group and 4.58 cm (median 4 cm) in the recurrent-metastasis group and statistically significant (P <0.001). In our study, the percentage of patients with tumor diameter 2 cm and over was 88.2% in the recurrent-metastasis group; whereas in the remission group this rate was 76% and statistically significant (p <0.001). Consistent with the literature, in our study, the recurrence-metastasis rate increased as the tumor diameter increased.

The number of metastatic lymph nodes is also a factor that affects the prognosis negatively. In patients with one to three lymph node positive patients, recurrence rate is lower than in patients with four or more lymph node positive patients and the likelihood of long-term survival is higher. The 5-year survival rate in nod negative patients is 70-80%, while the 5-year recurrence rate is approximately 20%. In the American National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, 24740 patients were examined and it was determined that as the lymph node involvement increased, the likelihood of recurrence increased and survival decreased and this correlation was found to be directly proportional to the increase in tumor size [6].

The percentage of N0 patients in our study was 39% in the remission group; and 14% in the recurrence-metastasis group. The percentage of patients with the number of invol. nodes 4 or more was 30.4% in the remission group and 55.7% in the recurrence-metastasis group and was statistically significant (p <0.001). The recurrent-metastasis rate increased as the number of involvement nodes increased.

Histopathologic subgroups of breast cancer can be grouped into three groups according to prognostic outcome. Good prognosis: mucinous, tubular, papillary. Moderate prognosis: medullary, invasive, lobular. Poor prognosis: infiltrative ductal (NOS = nototherwise specified), atypical medullary. Infiltrative ductal carcinoma is the most common of these histopathologic subgroups. In our study, 276 ductal (81%), 39 lobular (11%), 14 medullary (4%) and 11 other (3%) histologic types were evaluated in the remission group in the treatment group.

Of the 134 patients evaluated in the recurrence- metastasis group, 117 were ductal (87%), 5 were lobular (3%), 8 were medullary (6%) and 4 were other histologic types. The statistical difference between the two groups was significant (p = 0.061).

The percentage of lymphovascular invasion in our study was 46.4% in the remission group; in the recurrent metastasis group. A statistically significant difference (p <0.001) was found at the level of significance. Lymphovascular invasion in the recurrent-metastasis group was significantly higher.

In our study, chemotherapy start time was designed as 1 month before or 1 month later. The percentage of chemotherapy recipients in the early phase was 90.3%; 76% in the relapse-metastasis group and statistically significant (P <0.001). Chemotherapy started early in the majority of patients in the remission group.

The percentage of female patients in our study was 98.9%; The percentage of patients aged 40-70 years was 70.9%. These results supported the literature on the prevalence of women in breast cancer and the incidence in advanced age.

When the patients were evaluated from the procedure of operation, the breast conserving surgery was mostly performed in the remission group; Patients in the recurrence-metastasis group were more likely to have undergone a modified radical mastectomy. There was statistically significant difference between operation type and recurrence (p = 0.011). MRM was more recurring in constructions. This may be related to the fact that the recurrent patients are in a more advanced stage at the time of diagnosis.

Recurrence was observed in 244 patients followed by Takeuchi et al. And 1428 patients with breast cancer. When the factors affecting recurrence were evaluated by univariate analysis, there was a

correlation between tumor size, ER, PR positivity and time; in multivariate analysis, ER and PR positivity were found to be independent risk factors for recurrence development time [7].

In our study, patients who developed recurrence as a second subgroup analysis were analyzed after grouping as early and late recurrence based on 24 months. Kuhar and colleagues conducted an evaluation study in early post-operative breast cancer patients at the 10th postoperative year that lymphovascular invasion and ER positivity were independent prognostic factors for late recurrence; tumor size, grade, and nodal status did not predict prognostic value for late recurrence [10].

In a Canadian study, 2.5-year early recurrence in patients with adjuvant breast cancer was associated with nod-positivity and low ER positivity [11]. In our study, there was a statistically significant difference between late recurrence with increased ER positivity (p = 0,031) and late recurrence with increasing frequency of adjuvant hormonal therapy (p = 0.019).

The most common site of metastasis in breast cancer is bone, and this rate is up to 50% in follow-up. Bone metastasis was detected most frequently in our study (33.3%). It was observed consistent with the literature data.

A retrospective analysis of 691 patients with breast cancer followed up at the Dutch Cancer Institute of Bijker *et al*. Found a relationship between local recurrence and lymph node involvement and tumor size [8]. The risk of local regional recurrence increases with increasing tumor size. Tumor diameter is greater than 5 cm. In the study performed by Rosenman and colleagues, local recurrence was reported to be 8% in T1, 18% in T2, and 32% in T3 in patients with MRM or RM [9]. A study by Bidard and colleagues found a relationship between micrometastatic disease and local and distant metastases. There was no difference between micrometastatic disease and metastatic site [12]. In our study, there was no statistically significant relationship between tumor size and metastasis site (p> 0.05). When analyzed for nodal involvement, there was no difference in the location of metastases in the cases of lymph node involvement 0-9; distant metastasis was increased in patients with lymph node involvement of ≥10, and this was statistically significant (p = 0.034). There was statistically significant correlation between missing staging and local recurrence (p = 0.031). There was statistically significant correlation with bone metastasis in patients who had not undergone scintigraphy during staging (p = 0.006). This is the most common metastatic site in breast cancer, scintigraphic evaluation of the staging during the evaluation of the bone at the time of diagnosis of bone metastasis in patients will be important to not skip.

CONCLUSION

The factors determining the recurrence in patients with breast cancer were the tumor size, the number of lymph nodes involved, lymphovascular invasion, grade, incomplete staging and the time between surgery and chemotherapy was 1 month. The factors determining late recurrence were ER positivity and use of adjuvant hormonal therapy. Local recurrence was associated with inadequate staging and distant metastasis and a significant association between ≥10 lymph node.

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