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Retrospective evaluation of breast cancer patients with five or more axillary lymph node involvement achieving 5-year overall survival

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ABSTRACT

Objectives: The aim of this study was to analyze high risk breast cancer patients with involvement of five or more axillary lymph nodes with an overall survival of at least five years, and to determine the predictive and prognostic factors by comparing patients by recurrence/metastases status retrospectively.

Methods: From a total of 500 patients those were followed up in Adnan Menderes University, Medical Oncology department, 37 were eligible for the study; 23 were disease free and 14 had recurrence/metastases in the follow up period. The patients were analyzed, for demographical (such as age, menopausal status, obesity), anatomical and histological characteristics of tumor (primary tumor's diameter, stage, grade, Ki-67, hormon receptors and Her-2 status), treatment modalities and prognosis.

Results: Both number of metastatic lymph nodes and (metastatic/sampled) lymph node ratio were not significantly different between the recurrence-free and metastatic patients. In the recurrence-free patients both grade 3 (48% vs none, $p = 0.03$) and p53 negative tumors (64% vs 36%, $p = 0.036$) were significantly more than metastatic patients. Also in the recurrence free patients as compared to metastatic patients, adjuvant chemotherapy was applied more than 6 cycles (87% vs 43%, $p = 0.004$), the regimens included more taxane based regimens (91% vs 64%, $p = 0.042$), aromatase inhibitors were used higher (100% vs 75%, $p = 0.019$) and the period of tamoxifen treatment in switch regimens were shorter.

Conclusion: The results of this study suggested that, high risk breast cancer patients with involvement of five and more nodes that have the predictive factors as grade 3 and/or p53 negative tumors are propably more responsive to adjuvant treatments. Chemotherapy of more than 6 cycles, administering taxane based regimens and aromatase inhibitors in the adjuvant regimens may favourably effect the prognosis.

Keywords: breast cancer, lymph node metastases, predictive and prognostic factors

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Breast cancer is the most frequently diagnosed cancer in women, which consist of many clinical subtypes with distinct biological features [1]. Breast cancer patients, have different response patterns to various treatment modalities and clinical outcomes. Prognostic and predictive factors are critical for the selection of local or systemic therapies. These factors include, tumor histology, clinical and pathologic characteristics of the primary tumor (especially tumor size and tumor grade), axillary lymph node status,

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tumor hormone receptor (ER/PgR) expression, tumor Her-2 status, existance of metastatic disease , patient comorbid conditions, patient age and menopausal status [2].

Patients with metastatic lymph node involvement are the most often candidates for chemotherapy and if the tumor is hormone receptor positive, for the subsequent endocrine therapy [3]. Although multiple metastatic axillary lymph nodes are strong negative prognostic factor for disease recurrence and death from breast cancer, there have been a group of patients with extensive nodal involvement which have five or more years overall survival after local and systemic therapies.

The aim of this study was to analyze high risk breast cancer patients with involvement of five or more axillary lymph nodes with an overall survival of at least five years, and to determine the predictive and prognostic factors by comparing patients by recurrence/metastases status retrospectively.

METHODS

In this study, medical files and pathology reports of 500 breast cancer patients who were on follow up at Adnan Menderes University medical oncology department were screened retrospectively. Thirty-seven patients had breast surgery and axillary lymph node dissection with a final pathology report showing 5 or more metastatic axillary lymph node involvement. All of 37 patients had received adjuvant chemotherapy. Fourteen patients developed metastatic disease, while the other 23 patients were relapse free , after at least 5 years follow up.

Demographic characteristics, pathological features of primary tumor (size, grade, Ki-67, hormone receptor and Her-2 status, stage), treatment modalities (surgery, radiotherapy, chemotherapy, hormonotherapy) were recorded from medical files.

ER and PgR status were tested by immunohistochemistry, and a value ≥ 1% was considered as positive. Her-2 status was obtained by immunohistochemistry or fluorescent in situ hybridization (FISH). IHC 3+ and IHC 2+ that were FISH positive were classified as Her-2-positive tumors; IHC 2+ that were either FISH negative, or IHC 1+ were classified as HER2-negative tumors. Ki-67 levels over 14% are considered high; whereas levels below 14% were considered low. p53 levels considered as positive when > 10% of cells were positive regardless of the intensity.

Eligible patients had five and more metastatic axillary lymph node involvement, breast surgery for non metastatic breast cancer, and at least five years follow-up. Patients with synchronous distant metastases, and taking neoadjuvant treatment were excluded from the study.

Statistical Analysis

The data analysis was performed by using SPSS for Windows, version 22 (SPSS, Chicago, IL, USA). The normality of the distributions of continuous variables was determined via the Shapiro–Wilk test. The data were reported as the mean ± standard deviation or median and range where applicable. The differences in the results between the groups were compared by performing Student's t-test or the Mann–Whitney U test, where appropriate. The categorical data were analyzed by using Pearson's chi-square or Fisher's exact test, where appropriate. A $p < 0.05$ was considered as indicating statistical significance.

RESULTS

Between January 2010 and December 2014, 37 breast cancer patients were enrolled in the study. The baseline characteristics of the study subjects and tumors are summarized in Table 1. There were no difference between menopause status and obesity in patients with and without relapsed disease. Primary tumor was right-sided in 21 (57%) patients and left-sided in 16 (43%) patients. Upper-outer quadrant was the most frequent site for primary tumor.

Grade 3 tumors were higher in patients without recurrence or metastases. There was no significant difference between groups according to metastatic lymph node numbers,histology, pT stage and pN stage (Table 1).

Immunohistochemical characteristics of tumors are shown in Table 2. 87% of tumors were Luminal subtype (Luminal A and Luminal B). The most common subtype was Luminal B (65%). There was no significant difference between patients according to breast cancer molecular subtypes ($p = 0.517$). Patients

Table 1. Patient and tumor characteristics

Characteristics		Relapse free	Relapsed	*p* value
Age (years)		47 ± 9	46 ± 10	
Total lymph node		20 ± 6	20 ± 8	> 0.05
Metastatic lymph node		12 ± 6	13±6	> 0.05
Metastatic/total LN		0.61	0.66	> 0.05
Tumor side	Right	14 (70%)	7%30	> 0.05
	Left	16 (36%)	%64	
Histology	Ductal	21 (92%)	11 (79%)	> 0.05
	Lobular	1 (4%)	3 (21%)	
	Ductal+lobular	1 (4%)	0	
Tumor size	T1	6 (26%)	5 (36%)	> 0.05
	T2	14 (61%)	5 (36%)	
	T3	3 (13%)	5 (28%)	
Tumor grade	Grade 1	1 (4%)	1 (10%)	**< 0.03**
	Grade 2	10 (48%)	9 (90%)	
	Grade3	10 (48%)	0	
Lymph node stage	N2	8 (35%)	5 (36%)	> 0.05
	N3	15 (65%)	9 (64%)	
Perinodal invasion	Yes	13 (44%)	9 (64%)	> 0.05
	No	10 (56%)	5 (36%)	
Menopausal status	Premenopause	10 (43%)	5 (36%)	> 0.05
	Perimenapause	3 (14%)	2 (14%)	
	Postmenapause	10 (43%)	7 (50%)	
Body mass index (kg/m^2)	> 30	6 (26%)	3 (21%)	> 0.05
	< 30	17 (74%)	11 (79%)	

All values are median. Body mass index: weight/height^2

Table 2. Immunohistochemical features of tumors

		Relapse free	Relapsed	*p* value
ER	Negative	6 (26%)	4 (28%)	> 0.05
	Positive	17 (74%)	10 (72%)	
PgR	Negative	4 (17%)	2 (14%)	> 0.05
	Positive	19 (83%)	20 (86%)	
Her-2	Negative	12 (52%)	10 (71%)	> 0.05
	Positive	11 (48%)	4 (29%)	
Ki-67	Negative	8 (35%)	6 (43%)	**0.036**
	Positive	15 (65%)	8 (57%)	
p53	Negative	14 (64%)	5 (36%)	**< 0.05**
	Positive	8 (36%)	9 (64%)	
Tumor subtype	Luminal A	5 (22%)	3 (22%)	> 0.05
	Luminal B	15 (65%)	9 (64%)	
	Her-2	2 (9%)	0	
	Triple negative	1 (4%)	2 (24%)	

ER = estrogen receptor, PgR = progesterone receptor, HER2 = human epidermal growth factor receptor 2

Table 3. Adjuvant systemic treatments

		Relapse free	Relapsed	*p* value
Chemotherapy cycle		8 ± 1	6.4 ± 1.8	**0.001**
Duration of hormonal treatment (months)		75.7 ± 21.7	30.5 ± 21.4	**0.001**
Duration of tmx in switch (months)		22.2 ± 4	39.7 ± 14.6	**0.004**
Chemotherapy	< 6 cycle	3 (13%)	8 (57%)	**0.004**
	> 6 cycle	20 (87%)	6 (43%)	
Taxane regimen	Yes	21 (91%)	9 (64%)	**0.042**
	No	2 (9%)	5 (36%)	
Type of hormonal treatment	Tmx	0	3 (25%)	**0.019**
	AI	10 (50%)	4 (33%)	
	Switch	10 (50%)	3 (25%)	
	Other	0	2 (17%)	
Tmx in switch	< 36 month	10 (100%)	1 (33%)	**0.005**
	> 36 month	0	2 (67%)	

with relapse-free disease have higher rates of p53 negativity as compared with patients who developed metastases (Table 2).

Adjuvant treatment modalities were shown in Table 3. All patients received 3 to 6 cycles of antracycline based chemotherapy first and then, most of patients had taxane based chemotherapy subsequently. Total chemoterapy cycles were higher in recurrence free group. Duration of tamoxifen treatment was shorter in recurrence free group. Patients with recurrence free disease had received more taxane chemotherapy when compared with the others.

DISCUSSION

In this study, we retrospectively evaluated patients who were operated for breast cancer with a final pathology report of 5 or more metastatic lymph node involvement and achieved five year overall survival. All patients received adjuvant chemotherapy. We compared patients who were relapse free at 5 years, with patients who developed recurrence or metastases to analyze prognostic and predictive factors in this high risk patient population.

There are some well-defined risk factors for breast cancer development [4-9]. Breast cancer risk factors such as age, family history , smoking, oral contraceptive use, obesity were not different between groups. At the time of diagnosis, 15 (40%) of the patients were premenopausal, 5 (14%) were perimenopausal and 17 (46%) were postmenopausal and there was no difference in menopausal status between the two groups.

In the group without recurrence, 48% of the patients had grade 3 tumor, whereas the control group had no grade 3 tumor. Although, high tumor grade has a negative impact on the natural course of the disease, high grade tumors may be more sensitive to chemotherapy and radiotherapy. In a retrospective study of 183 patients who received neoadjuvant anthracycline and taxane based chemotherapy, there was a significant correlation between pathologic response and tumor p53 expression and tumor grade [10].

Primary tumor localization was right breast in 70% of the patients in the relapse-free group, whereas left breast in 64% of the recurrent patients. The difference in right/ left breast side was statistically

significant; but there was no difference according to the quadrant. Karatas *et al*. [11] studied 305 non-metastatic women with pathological N3 (pN3) nodal involvement and showed that, left laterality in patients with pN3 non-metastatic breast as an independent risk factor associated with distant metastases and axial bone involvement compared with right laterality.

Tumor diameter is one of the important prognostic factor for the requirement for adjuvant therapy [12, 13]. The risk of recurrence or distant metastasis increases linearly with the increase in tumor size. Tumor diameter is the main prognostic factor, especially in node-negative patients, while this effect decreases in node-positive patients. Many studies have shown an inverse relationship between tumor size and metastasis or survival. There were no significant differences in the number of foci of primary tumor, mean diameter, and T-stage between the groups with and without recurrent disease. Because of the high number of metastatic lymph nodes in our study population, the contribution of tumor diameter to prognosis of these patients was considered to be low. The number of metastatic lymph nodes in breast cancer is considered to be one of the important prognostic factors. In an analysis based on Holland cancer records, 23.315 patients with node-positive breast cancer treated between 1999 and 2005 were evaluated. The overall 5-year survival was 78% in the whole population while 84% in cases with 1-3 metastatic lymph node involvement, and 55% in cases with > 10 metastatic lymph node involvement [14]. In this study; there was no significant difference between groups in terms of presence of perinodal invasion and N stage. This result suggests that groups with relapse free and recurrent patients are homogeneous in terms of lymph node metastasis and that other predictive and prognostic factors are important in our cases.

Hormone receptor positivity was high in the patients (87%), especially Luminal B was the most common tumor type but there was no significant difference between the two groups in terms of tumor subtype. There was no difference in the Ki-67 and Her-2 levels between the groups.

The higher incidence of p53 negativity, suggests that the sensitivity of adjuvant therapy is higher in the relapse free group.

Chemotherapy is the basis of adjuvant treatment in cases, with axillary lymph node metastases. The total number of chemotherapy cycles was found to be higher in the recurrence-free group. When the total number of chemotherapy cycles was categorized as < 6 and > 6, it was found that more patients in the recurrence free group had 6 or more chemotherapy cycles. This finding indicates the importance of the number of chemotherapy cycles in high-risk locally advanced breast cancer.

Taxanes have been extensively given as adjuvant chemotherapy for the treatment of operable breast cancer, particularly in high risk, node-positive patients [15]. Taxane treatment was significantly higher in the relapse free patients than recurrent patients. This suggests the importance of taxane after anthracycline treatment in high-risk breast cancer.

All luminal A and B patients received hormonal treatments. Aromatase inhibitor and switch (aromatase inhibitor after tamoxifen) treatments were in higher in recurrence free patients.

The use of more aromatase inhibitors than tamoxifen may be one of the positive prognostic factors in relapse free patients. The duration of the hormonal treatment was shorter in recurrence free group and it was considered to be related with switching patients to another treatment modality 'mostly chemotherapy', after recurrence.

Limitations

Our study has some limitations. First; this study had a relatively small number of patients and second has a retrospective nature.

CONCLUSION

In conclusion, grade 3 tumor and/or p53 negativity in high-risk locally advanced breast cancer can be used as predictive factors for adjuvant treatment response. Taxane treatment significantly improved clinical outcome. We believe that validation of these results in larger series with similar characteristics may be useful in local advanced breast cancer treatment.

Authorship Declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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