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ORIGINAL ARTICLE

The Effect of Adjuvant Therapies for Recurrence in Stage I Breast Cancer Patients: A Single Centre Experience

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OBJECTIVE

Breast cancer is the most diagnosed cancer in females. Cancer screening programs increase the detection of early-stage breast cancer. This study aimed to assess the long-term outcomes and the effect of adjuvant therapies for recurrence in stage I breast cancer patients.

METHODS

We recorded clinicopathological and treatment features of the stage I breast cancer patients and evaluated long-term outcomes retrospectively. Kaplan-Meier analysis and Cox regression analysis were used for recurrence and overall survival.

RESULTS

308 patients with stage I breast cancer were involved in the study. The average age was 52 (range 21-81). The median follow-up was 99 (12-380) months. Forty-three (14%) patients were aged over 65, and 162 (52.7%) patients were postmenopausal. ER, PR, and HER2 receptor positivity were 78.9%, 60.8%, and 14.3%, respectively. Lumpectomy plus adjuvant radiotherapy was performed in 82.1% of the patients, and mastectomy in 10.7% of the patients for primary treatment. The patients received adjuvant chemotherapy (42.5%) and adjuvant hormonal therapy (79.9%). Recurrence (local-47.8%, metastatic-52.2%) occurred in 23 (7.5%) patients. In multivariate Cox regression analysis, we found that primary treatment (lumpectomy + adjuvant RT or mastectomy) (p=0.614), surgical margin status (p=0.495), adjuvant chemotherapy (p=0.259), and adjuvant hormonal therapy (p=0.289) were not statistically significant factors for recurrence. However, aged over 65 years (p=0.002) was statistically significant.

CONCLUSION

In this study, we showed long-term outcomes in stage I breast cancer patients. It was shown that the primary treatment type (lumpectomy + adjuvant RT or mastectomy) was not different in terms of recurrence. In addition, it was determined that adjuvant chemotherapy did not provide benefit for recurrence in stage I breast cancer patients in our results. For this reason, in patients with stage I cancer, more care should be taken in the decision of adjuvant therapy.

Keywords: Adjuvant; breast cancer; chemotherapy; radiotherapy; stage I.

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INTRODUCTION

Breast cancer is the most frequently detected malignancy in females and is the second most common malignancy-related death cause in females.[1] In early-stage breast cancer (ESBC) patients, the primary treatment is surgery, but in the long term, adjuvant local radiotherapy or systemic therapies are applied to prevent micrometastases and recurrence. In patients with ESBC, the benefit and harm ratio is taken into account when deciding on adjuvant treatment after surgery. Both adjuvant radiotherapy and systemic therapies (chemotherapy and hormone therapy) can cause local and systemic side effects in the short and long term. Adjuvant treatment planning can be done according to different biological subtypes in breast cancer. Adjuvant endocrine therapy is used in patients with estrogen receptor positivity, and adjuvant therapies targeting HER2 are used in patients with HER2-positive tumors. In addition, it has been shown that the use of trastuzumab emtansine in HER2-positive breast cancer patients who were operated after neoadjuvant chemotherapy and remained residual tumor, and the use of adjuvant capecitabine in triple-negative breast cancer patients reduced recurrence.[2,3]

Although there are many factors that determine the prognosis in breast cancer, early diagnosis of the disease is one of the most essential factors that ensure high survival rates.[4] In the Early Breast Cancer Trial Collaborative Group (EBCTCG) meta-analysis, which evaluated the effects of adjuvant treatments on survival in ESBC and was published in 2012, patients who received anthracycline-containing chemotherapy regimens compared to those who did not receive treatment; the recurrence rate was reduced by 8%, the breast cancer-related mortality rate by 7%, and the overall mortality rate by 5%.[5] Although the tumor stage at the time of diagnosis in breast cancer may vary according to race, age, and socio-economic status, approximately 48% of the patients are diagnosed with stage I disease.[6] The primary therapy in stage I breast cancer is surgery, and the type of surgery may vary depending on the location of the tumor, breast size, and genetic characteristics of the tumor. It has been shown that lumpectomy plus radiotherapy has similar results with only mastectomy in terms of survival in stage I breast cancer in long-term follow-up.[7,8] For this reason, minimally invasive surgery is generally preferred in stage I breast cancer. In the study, we aimed to evaluate the treatment characteristics and the adjuvant treatment effects on long-term outcomes in patients with stage I breast cancer.

MATERIALS AND METHODS

Patients and Data Collection

This study was planned as a retrospective cohort study. Prior to the study, academic committee approval was obtained, and the study was conducted according to the good clinical practice guidelines. Stage I breast cancer patients diagnosed and treated between 1988 and 2018 were included in the study. The patients to be included in the study were identified through the hospital data processing system. Patients with incomplete data for study analysis were not included in the study. The treatment features of the patients (surgery, chemotherapy, radiotherapy, and endocrine therapy) and the recurrence status during the follow-up period were also noted. All patients' tumor features were assessed in a standardized pathology laboratory. The Bloom-Richardson Grading System was used to determine the tumor's histological grade. The immunohistochemistry (IHC) technique was used to assess estrogen receptor (ER) and progesterone receptor (PR). If the HER2 receptor IHC score was 3, or positive using the in-situ hybridization technique, HER2 positivity was deemed significant. Tumor stages were established with the eighth edition of the American Joint Committee on Cancer.

The living status of the patients was questioned through the death notification system of the Ministry of Health. From diagnosis time to death time from any cause was defined as overall survival (OS). Disease-free survival (DFS) was accepted as the time from surgery to the recurrence of the disease. Univariable and multivariable analyses were done on clinical, pathological, and treatment-related factors for DFS.

Statistical Analysis

The statistics of the study were performed via SPSS 29 (IBM, Armonk, NY, USA). Continuous variables in the study were represented by median (as well as minimum and maximum values) value numbers and percentages, while categorical variables were described by numbers and percentages. For survival analysis, the Kaplan-Meier method was employed. Univariate and multivariate analysis with the Cox regression method was performed on clinical and pathological factors for recurrence. When the p-value was under 0.05, results were accepted as statistically significant, and the probability ratio was calculated.

Table 1 Patients characteristics

	n	%	Valid (%)		n	%	Valid (%)
Age at diagnosis (years)				PR status			
<65	265	86		Positive	187	60.8	63.6
≥ 65	43	14		Negative	107	34.7	36.4
Menopausal status				Unknown	10	4.5	
Premenopausal	138	44.7	46	HER2 overexpression			
Postmenopausal	162	52.7	54	Positive	44	14.3	15.4
Unknown	8	2.6		Negative	241	78.2	84.6
Primary tumor locations				Unknown	23	7.5	
Left side	159	51.6	51.7	Tumor grade			
Right side	145	47.1	47.2	Grade 1	61	19.8	21.4
Bilateral	3	1	1.1	Grade 2	134	43.5	47
Unknown	1	0.3		Grade 3	90	29.2	31.6
Histological type				Unknown	23	7.5	
IDC	221	71.8	72	Lymphovascular invasion			
Other types (Invasive lobular carcinoma Mixed type, micropapillary, etc.)	86	27.9	28	Yes	59	19.2	21.2
				No	219	71.1	78.8
Unknown	1	0.3		Unknown	30	9.7	
pT status				Surgical margin status			
1a	18	5.8		Positive	24	7.8	7.9
1b	72	23.4		Negative	278	90.3	92.1
1c	218	70.8		Unknown	6	1.9	
ER status				Recurrence			
Positive	243	78.9	81.5	No	285	92.5	
Negative	55	17.9	18.5	Local	11	3.6	
Unknown	10	3.2		Metastatic	12	3.9	

n: Number of patients; IDC: Invasive ductal carcinoma; pT: Pathologic tumor size; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2

RESULTS

Patient Characteristics and Treatment Approaches

The study analyses were performed with data from 308 patients. The average age of the patients was 52 (21-81). The most seen histopathological type was invasive ductal carcinoma (IDC) (71.8%). ER positivity was 78.9%, and HER2 positivity was 14.3%. The rate of patients with grade 3 tumors was 29.2%. The general features of the patients are presented in Table 1. Lumpectomy and adjuvant radiotherapy were applied to 82.1% of the patients as primary treatment. Mastectomy was performed in 10.7% of the patients. The ratio of patients who received adjuvant chemotherapy was 42.5%, and the rate of patients who received adjuvant endocrine therapy was 79.9%. The average dose of radiation was 50 Gy in 25–28 fractions. Adjuvant chemotherapy was mostly performed using taxane- and anthracycline-based chemotherapy. Only 28 of 44 patients with HER2 positivity could receive adjuvant trastuzumab because some patients had been diagnosed in the pre-trastuzumab period. Patients with hormone-positive tumors had received a median of 5 years of endocrine therapy (either tamoxifen or aromatase inhibitor or sequentially). The treatment-related features of the patients are shown in Table 2.

Survival Outcomes

The average follow-up was 99 months. During the follow-up, 24 patients died. The 5-, 10-, and 20-year OS rates were 97.5%, 90.1%, and 75.9%, respectively (Fig. 1). During the follow-up period, recurrence occurred in 23 (7.5%) patients. 47.8% of the recurrences were local, and 52.2% of them were metastatic disease. The 5-, 10-, and 20-year DFS rates were calculated as 96.1%, 92.7%, and 75.6%, respectively (Fig. 2). Clinical, pathological, and treatment-related factors for DFS were analyzed. Age (p=0.002) was determined to be statistically significant. Primary treatment type (p=0.614), surgical margin status (p=0.495), adju-

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Table 2 Treatment approaches for the patients

	n	%	Valid (%)
Breast surgery type			
Mastectomy	33	10.7	
Lumpectomy	275	89.3	
Lymph node surgery			
Sentinel node biopsy	260	84.4	86.7
Axillary lymph node dissection	40	13	13.3
Unknown	8	2.6	
Primary treatment			
Lumpectomy+RT	253	10.7	88.5
Mastectomy	50	10.7	11.5
Unknown	22	7.1	
Adjuvant radiotherapy			
Yes	265	86	91.1
No	26	8.5	8.9
Unknown	17	5.5	
Adjuvant chemotherapy			
Yes	131	42.5	44.4
No	164	53.3	55.6
Unknown	13	4.2	
Adjuvant tratuzumab			
Yes	28	63.7	
No	16	36.3	
Adjuvant hormone therapy			
Yes	246	79.9	83.7
No	48	15.6	16.3
Unknown	14	4.5	

n: Number of patients; RT: Radiotherapy

vant chemotherapy (p=0.688), and adjuvant hormone therapy (p=0.150) were not found statistically significant in multivariate analysis for DFS (Table 3).

DISCUSSION

In our study, we showed long-term outcomes for stage 1 breast cancer. In stage I (T1a and T1b) breast cancer patients who do not receive adjuvant therapy, it was shown that the 10-year relapse-free survival was above 90%, and it has been shown that the most important pathological factors determining prognosis were the grade of tumors and lymphovascular invasion (LVI).[9] In our study, the long-term results of stage I breast cancer patients for DFS and OS were excellent, although the prognostic significance of tumor grade and LVI status was not detected. This situation can be explained by the relatively limited number of patients in our study and the number of recurrences. Also, we did not detect any difference in terms of recurrence between the lumpectomy + radiotherapy group and the mastectomy group as primary treatment in stage I breast cancer. Similar to our study, in the EORTC 10801 study, overall survival and distant metastasis results of stage 1–2 breast cancer patients who underwent breast-conserving surgery plus radiotherapy and who underwent modified radical mastectomy were found to be similar in the 20-year follow-up.[10] Some studies have been published showing that lumpectomy (with or without radiotherapy) is equal or superior to mastectomy in terms of survival outcomes in the selection of appropriate treatment in ESBC. In a population-based study from the Netherlands, lumpectomy plus radiotherapy was compared with mastectomy in ESBC, and the breast-conserving surgery plus radiotherapy group was found superior for 10-year OS and distant metastasis (only T1 group).[11] In another study published by Hwang et al.,[12] the patients with ESBC treated with breast-conserving therapy were found to be better in patients who underwent mastectomy for disease-specific survival rates. Also, in a study published by Agarwal et al.,[13] groups of patients with ESBC who were treated with breast-conserving therapy, mastectomy, and mastectomy with radiation were compared, and the patient group who was treated only with breast conservation therapy was found better for survival (Ten-year OS results; p<0.001, 94%, 90%, and 83%, respectively).

In patients with ESBC, overtreatment can be applied to some patients if the adjuvant treatment decision is not made according to the appropriate criteria for patient selection. There are two well-defined markers that show benefit from adjuvant therapy in patients with ESBC: ER (for endocrine therapy) and HER2 receptor (for HER2-directed therapy). In a meta-analysis by the EBCTCG group, it was shown that the use of tamoxifen for five years in ER-positive breast cancer patients reduced the risk of breast cancer-related recurrence and death for 15 years.[14] There are many studies showing the benefit of different adjuvant endocrine therapies in terms of survival in ESBC. Similarly, the addition of trastuzumab to adjuvant chemotherapy in HER2-positive breast cancer patients has been shown to reduce the risk of death by 33%.[15] In our study, we did not show any benefit of adjuvant chemotherapy for DFS in stage I breast cancer. Adjuvant chemotherapy has been shown to increase survival rates in patients with ESBC in the literature. Since the chemotherapy response is heterogeneous in patients, genetic tests that predict response to treatment are used in the decision of adjuvant chemotherapy in patients with ER-positive HER2-neg-

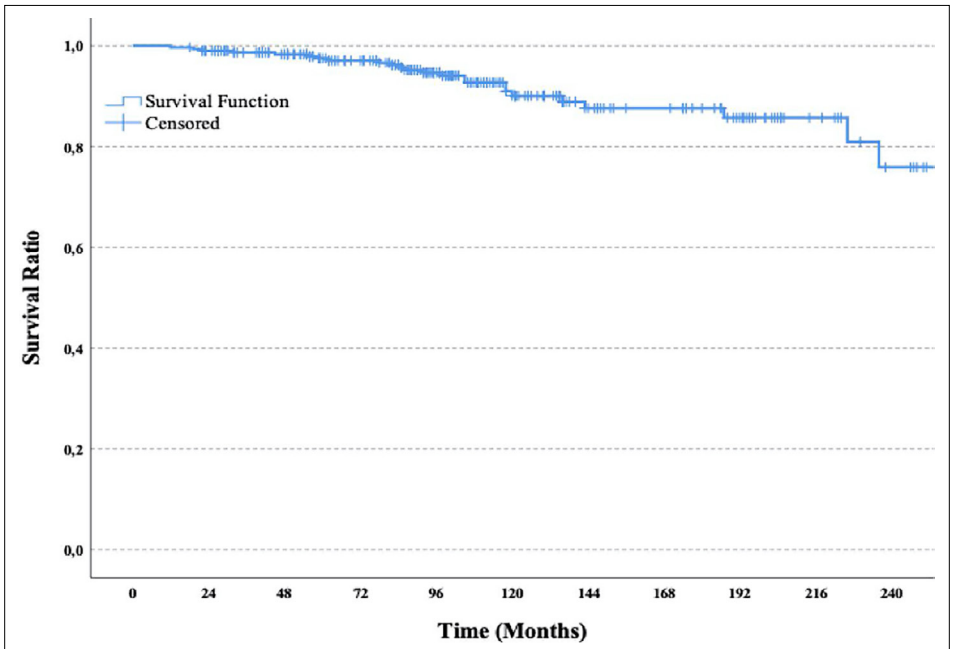

Fig. 1. Kaplan-Meier Curve for OS in the patients.
OS: Overall survival.

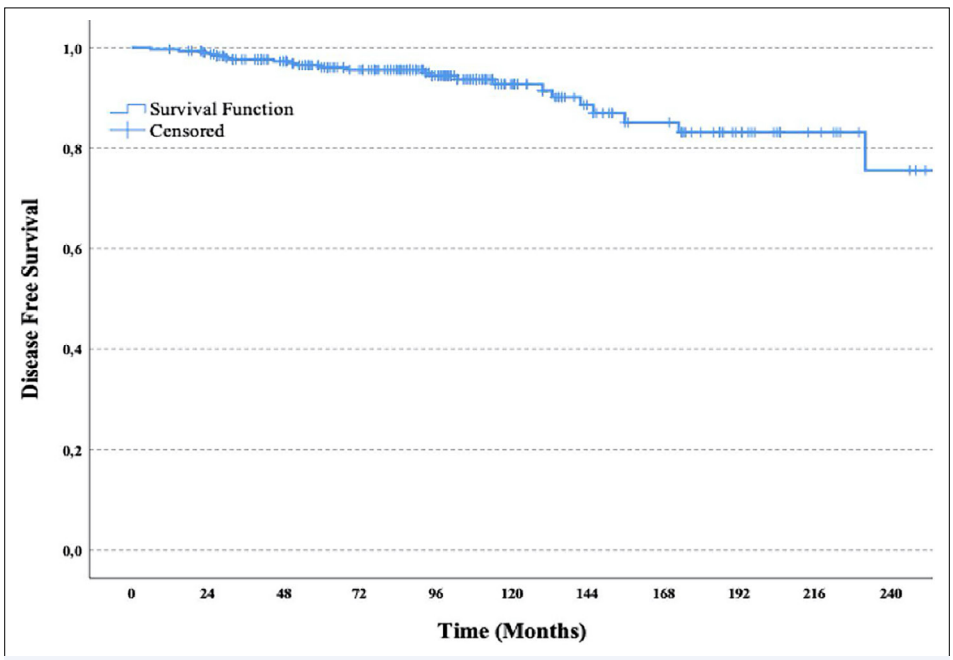

Fig. 2. Kaplan-Meier Curve for DFS in the patients.
DFS: Disease-free survival.

ative tumors. Prognostic measurement methods such as Oncotype DX, Predictor Analysis of Microarray 50, EndoPredict, Breast Cancer Index, and MammaPrint have been developed to calculate the risk of recurrence in ESBC patients with ER-positive and HER2-negative tumors.[16] Oncotype DX 21-gene Recurrence Score (RS) is one of the best-validated modalities in adjuvant chemotherapy decisions. Only in patients with early-stage ER-positive HER2-negative breast cancer with RS ≥ 25 or RS ≥ 31 was it shown that adding chemotherapy

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Table 3 Univariate and multivariate analysis for DFS in the patients with stage I breast cancer

	Univariate analysis	Multivariate analysis	
	p	p	Odds ratio CI 95%
Age			
<65 vs. ≥65	**0.001**	**0.002**	4.82 (1.82–12.83)
Menopausal status			
Premenopousal vs. postmenopausal	0.340		
Primary tumor locations			
Left side vs. right side	0.717		
Histological type			
IDC vs. other types	0.121		
pT status			
1a vs. 1b and 1c	0.520		
ER status			
Positive vs. negative	0.805		
HER2 overexpression			
Positive vs. negative	0.396		
Tumor grade			
Grade 1 vs. grade 2 and grade 3	0.241		
Lymphovascular invasion			
Yes vs. no	0.886		
Surgical margin status			
Negative vs. positive	0.753	0.495	1.56 (0.43–5.65)
Primary treatment			
Lumpectomy+RT vs. mastectomy	0.245	0.614	1.35 (0.41–4.46)
Adjuvant tratuzumab			
Yes vs. no	0.578		
Adjuvant chemotherapy			
No vs. yes	0.688	0.259	1.70 (0.67–4.29)
Adjuvant hormone therapy			
No vs. yes	0.150	0.289	1.56 (0.43–10.43)

Multivariate analysis test model p=0.005. DFS: Disease-free survival; CI: Confidence interval; IDC: Invasive ductal carcinoma; pT: Pathologic tumor size; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; RT: Radiotherapy

to endocrine therapy improved survival outcomes.[17] Similarly, measurement methods such as PAM50 risk of recurrence score, EndoPredict, Breast Cancer Index, MammaPrint, and Mammostrat that predict the response to adjuvant therapy in patients with HER2-negative and HER2-positive ESBC have strengths and weaknesses and need to be validated in the future.[18]

The study had some limitations due to its retrospective character. The patient group was heterogeneous, and some data were missing. Due to the small number of patients with recurrence, multivariate analysis was performed with a limited number of factors. Some of the HER2-positive patients could not use trastuzumab because they had been diagnosed in the pre-trastuzumab period.

CONCLUSION

In our study, we showed that the primary treatment type (lumpectomy + adjuvant RT or mastectomy) has similar outcomes for stage I breast cancer patients. We

did not find any difference in terms of recurrence between stage I breast cancer patients who received adjuvant chemotherapy and those who did not. In addition, we found that patients over the age of 65 are more at risk for recurrence. Our study contributes to the literature by providing long-term outcomes in stage I breast cancer patients. In the future, with the further development and increased availability of genetic recurrence risk scoring methods, the decision for adjuvant treatment in ESBC will be made more accurately.

Ethics Committee Approval: The study was approved by the İstanbul University Institute of Oncology Ethics Committee (no: 1723130, date: 07/04/2023).

Authorship contributions: Concept – İ.D., A.A.; Design – İ.D., A.A.; Supervision – İ.D., N.K., E.A., N.P., F.F., N.A., S.E., K.İ., S.Ö., M.T., H.K., N.C., S.K., M.M., V.Ö., P.S., A.İ., A.A.; Materials – İ.D., N.K., E.A., N.P., F.F., N.A., S.E., K.İ., S.Ö., M.T., H.K., N.C., S.K., M.M., V.Ö., P.S., A.İ., A.A.; Data collection and/or processing – İ.D., N.K., E.A., N.P., F.F., N.A., S.E., K.İ., S.Ö., M.T., H.K., N.C., S.K., M.M., V.Ö., P.S., A.İ., A.A.; Data analysis and/or interpretation – I.D.; Literature search – I.D.; Writing – İ.D., N.K., E.A., N.P., F.F., N.A., S.E., K.İ., S.Ö., M.T., H.K., N.C., S.K., M.M., V.Ö., P.S., A.İ., A.A.; Critical review – İ.D., N.K., E.A., N.P., F.F., N.A., S.E., K.İ., S.Ö., M.T., H.K., N.C., S.K., M.M., V.Ö., P.S., A.İ., A.A.

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