Clinical and pathological differences of breast cancer in younger and elderly patients

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Clinical and pathological differences of breast cancer in younger and elderly patients.

AIM: *It is known that breast cancers seen in younger and elderly patients have a worse prognosis than the disease seen in middle age. This study aimed at revealing the clinical and pathological differences of the disease and investigating the factors that may have an effect on survival and disease-free survival in very young and elderly female patients who were treated and followed up for breast cancer in our clinics.*
PATIENTS AND METHOD: *The data of female patients who were diagnosed with breast cancer in our clinics between January 2000 and January 2021 were analyzed. Patients aged 35 years and below were assigned to younger group, while those aged 65 years and over were assigned to the elderly group. Clinical and pathological data of groups were analyzed.*
RESULTS: *The results of this study demonstrated no difference in mortality rates and overall survival compared to younger patients, despite the comorbidities and short life expectancy of elderly patients. Moreover, younger patients were found to have a larger tumor size at diagnosis, a higher recurrence rate, and shorter disease-free survival compared to elderly patients. Furthermore, young age was associated with an increased risk of recurrence.*
CONCLUSION: *The data of our study reveals that breast cancer seen in younger patients has a worse prognosis than in elderly patients. There is a need for large-scale randomized controlled studies to reveal all the underlying causes and to develop more effective treatment strategies in order to avoid the poor prognosis of young age-onset breast cancers.*

KEY WORDS: Breast cancer, Disease-free survival, Elderly patients, Overall survival, Prognosis, Younger patients

Introduction

Breast cancer is the most common type of malignancy in women and the second leading cause of cancer-related deaths worldwide [1,2]. The incidence of breast cancer has been reported to increase in recent years, especially in individuals under 35 years of age [3].

Breast cancers diagnosed at younger ages are known to have a more aggressive biological structure for reasons such as lower expression of hormone receptors, more frequent vascular invasion, poorer differentiation, and higher proliferation [4]. However, it is still a matter of debate whether young age is an indicator of a poor prognosis for breast cancer. Besides studies showing the negative effects of younger age on prognosis, there are also publications reporting no effect and even positive effects [5-8].

On the other hand, one-third of breast cancer cases worldwide are diagnosed in individuals aged 65 and over. Breast cancers appear to have a more moderate biological structure in elderly individuals [9].

More frequent hormone receptor positivity, less frequent c-erbB-2 overexpression, lower-grade tumors, and lower proliferative indices are indicators of this moderate biological structure [10]. However, it is not always possible to use standard treatment approaches for the elderly as

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they present with larger and advanced tumors, have advanced age, and accordingly a higher prevalence of comorbidities [9]. These and similar factors may adversely affect survival in elderly patients [11]
This study aimed at revealing the clinical and pathological differences of the disease and investigating the factors that may have an effect on survival and disease-free survival in very young and elderly female patients who were treated and followed up for breast cancer in our clinics.

Patients and Method

The data of 1102 female patients who were diagnosed with breast cancer, treated, and followed up in our clinics (Necmettin Erbakan University Meram Faculty of Medicine and Republic of Turkey Ministry of Health Karaman Training and Research Hospital General Surgery clinics) between January 2000 and January 2021 were retrospectively analyzed.
Patients aged 35 years and below (119 patients) were assigned to the younger group (Group 1), while those aged 65 years and over (128 patients) were assigned to the elderly group (Group 2).
Demographic data, surgical and/or medical treatments, clinical and histopathological findings of the tumor, long-term recurrence and mortality rates, overall survival, and disease-free survival of patients who met the study criteria and were included in the study were evaluated.
The differences between Group 1 and Group 2 in terms of these data and the variables that may have an effect on overall survival and disease-free survival were statistically analyzed.

Statistical Analysis

The analyses of the study data were carried out using the SPSS (Statistical Package for the Social Sciences, IBM Corp. Armonk, NY, USA) version 21.0 software package. The level of error was set at $p<0.05$ for all analyses. The normality of data distribution was evaluated using the Kolmogorov-Smirnov test.
Frequency table results were given for categorical variables and descriptive measures for numerical variables (mean ± st. deviation or median (min-max) in non-parametric cases). Student's t-test or Mann-Whitney U test was used to compare differences between the two groups. Chi-square analysis was used to test whether categorical variables were related or not.
Overall survival and disease-free survival were estimated using the Kaplan-Meier method. The log-rank test was used to determine whether there was a difference between the groups in terms of these variables. Risk factors that may affect overall survival and disease-free survival were analyzed using Cox's proportional hazards model.

Results

Presents a summary of the comparative basic demographic and clinical data of the patients included in the study (Table I). According to the Kolmogorov-Smirnov normality test, no variable from the numerical data of 119 patients in Group 1 and 128 patients in Group 2 who met the inclusion criteria was normally distributed ($p<0.05$). The median age was 32 (range, 24-35) years in Group 1, while it was 71 (range, 65-105) years in Group 2. Only 9 (7.6%) of the younger patients had comorbidities, whereas 96 (75%) of the elderly patients had any comorbidity ($p<0.001$). The most common comorbidity in the younger group was diabetes mellitus 5 patients (4.2%), while hypertension (68 patients (53.1%) and diabetes mellitus (39 patients (30.5%) were noted as the most common comorbidities in the elderly group. None of the patients in Group 2 reported alcohol use, while only 2 (1.7%) patients in Group 1 had a history of alcohol use ($p=0.14$). Sixteen (13.4%) patients in the younger group and 5 (3.9%) patients in the elderly group were smokers ($p=0.007$). The analysis of patients for secondary malignancy showed that 3 (2.5%) patients in Group 1 and 5 (3.9%) patients in Group 2 had a secondary malignancy ($p=0.53$). The analysis of patients for family history of malignancy revealed no statistically significant difference between the groups (29 (24.4%) and 21 (16.4%) patients had a family history of malignancy, respectively) ($p=0.12$). The disease was diagnosed during pregnancy in 4 (3.4%) patients in the younger group. Ninety-nine (82.3%) patients in Group 1 and 116 (90.6%) patients in Group 2 had a history of childbirth. There was no statistically

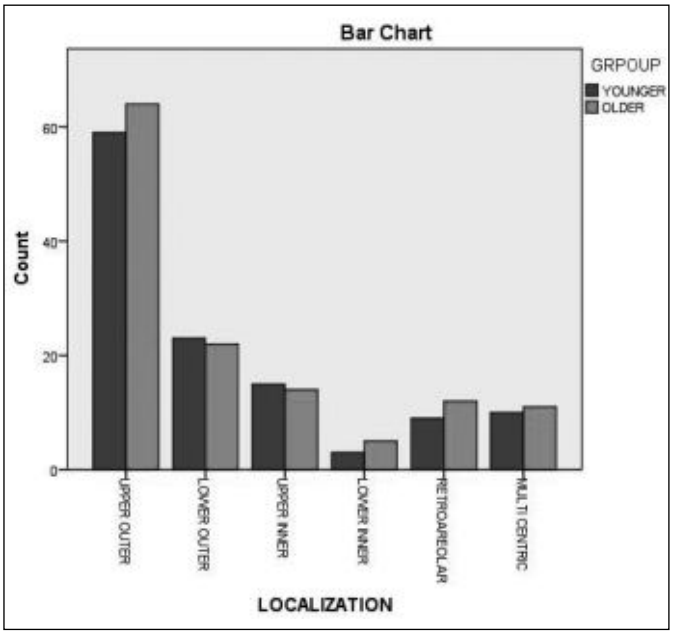

Fig. 1: Bar chart showing the localization of the tumors in both groups ($p = 0.76$).

Table I - *Analysis and comparison of demographic and some clinical characteristics between the younger and elderly breast cancer patients.*

	Younger Group N (%)	Elderly Group N (%)	P value (chi square)
Age	32 (24-35)	71 (65-105)	<0.001
Follow up time (month)	41 (4-240)	34 (3-145)	0.26
Recurrence time	30 (2-210)	31 (3-108)	0.99
Comorbidity			
No	110 (92.4%)	32 (25%)	<0.001
Yes	9(7.6%)	96 (75%)	
Alcohol			
No	117 (98.3%)	128 (100%)	0.14
Yes	2 (1.7%)	0 (0%)	
Smoking			
No	103 (86.6%)	123 (96.1%)	0.007
Yes	16 (13.4%)	5 (3.9%)	
Malignancy in family			
No	90 (75.6%)	107 (83.6%)	0.12
Yes	29 (24.4%)	21 (16.4%)	
Childbirth			
No	20 (16.8%)	12 (9.4%)	0.08
Yes	99 (83.2%)	116 (90.6%)	
Tumor Side			
Right	58 (48.7%)	58 (45.3%)	0.77
Left	60 (50.4%)	68 (53.1%)	
Bilateral	1 (0.8%)	2 (1.6%)	
Tumor localization			
Upper outer	59 (49.6%)	64 (50%)	
Lower outer	23 (19.3%)	22 17.2%)	
Upper inner	15 (12.6%)	14 (10.9%)9	0.97
Lower inner	3 (2.5%)	5 (3.9%)	
Central	9 (7.6%)	12 (9.4%)	
Multi centric	10 (8.4%)	11 (8.6%)	
Metastasis in diagnosis			
Bone	7 (50%)	9 (42.9%)	
Liver	3 (21.4%)	5 (23.8%)	0.55
Lung	0 (0%)	3 (14.3%)	
Multi organ	3 (21.4%)	2 (9.5%)	
Others	1 (7.1%)	2 (9.5%)	
Local recurrence			
No	114 (95.8%)	127 (99.2%)	0.08
Yes	4 (4.2%)	1 (0.8%)	
Metastasis in follow up			
Bone	6 (14.3%)	2 (9.5%)	
Liver	2 (4.8%)	3 (14.3%)	0.007
Lung	1 (2.4%)	6 (28.6%)	
Multi organ	27 (64.3%)	10 (47.6%)	
Others	6 (14.3%)	0 (0%)	
Recurrence			
No	78 (65.5%)	107 (83.6%)	0.001
Yes	41 (34.5%)	21 (16.4%)	
Mortality			
No	108 (90.8%)	111 (86.7%)	0.31
Yes	11 (9.2%)	17 (13.3%)	

significant difference between the groups in terms of childbirth (p=0.82).

The analysis of the diagnosed tumors in terms of locations revealed a higher frequency on the left side in both groups (50.4% (n=60), 53.1% (n=68), respectively). Only 1 (0.8%) patient in Group 1 and 2 (1.6%) patients in Group 2 had bilateral involvement. Given the quadrant of tumor location, the upper outer quadrant was the most common site of involvement in both groups (59 (49.6%) and 64 (50%) patients, respectively), followed by lower outer quadrant (19.3% (n=23) vs. 17.2% (n=22), upper inner quadrant (12.6% (n=15) vs. 10.9% (n=14), retroareolar area (7.6% (n=9) vs. 9.4% (n=12) and lower inner quadrant (2.5% (n=3) vs. 3.9% (n=5). Multicentric involvement was observed in 10 (8.4%) patients in the younger group and 11 (8.6%) patients in the elderly group (Fig. 1).

There was no statistically significant difference between the groups in terms of the side or quadrant of tumor location (p=0.77 and p=0.76, respectively).

Considering diagnostic biopsy methods, tru-cut biopsy was the most frequently used method in both groups. This was followed by excisional and fine needle biopsy, respectively. There was no difference between the groups in terms of the biopsy methods used (p=0.82). The most common histological type was infiltrative ductal carcinoma in both groups (74.8% (n=89) of the patients in Group 1 and 78.9% (n=101) of the patients in Group 2), followed by mixed-type tumors consisting of a combination of infiltrative ductal and infiltrative lobular carcinoma (8.4% (n=10) of the patients in Group 1, and 7.8% (n=10) of the patients in Group 2), and infiltrative lobular carcinoma (5% (n=6) of the patients in

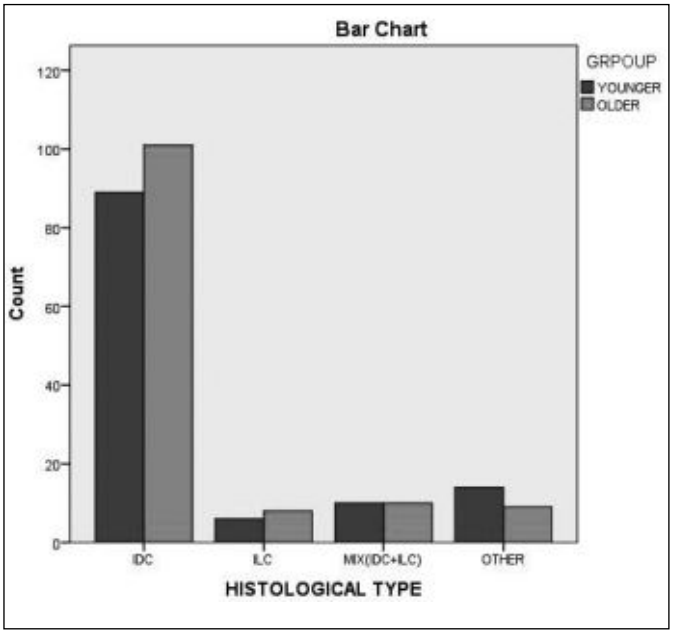

Fig. 2: Bar chart showing the histological types of the tumors in both groups (p = 0.61).

Table II - *Analysis and comparison of pathological characteristics between the younger and elderly breast cancer patients.*

	Younger Group N (%)	Elderly Group N (%)	P value (chi square)
T stage			
T1	16 (14.8%)	26 (23.9%)	
T2	64 (59.3%)	70 (64.2%)	0.02
T3	24 (22.2%)	9 (8.3%)	
T4	4 (3.7%)	4 (3.7%)	
N stage			
N0	34 (33.3%)	40 (39.6%)	
N1	28 (27.5%)	25 (24.8%)	0.11
N2	28 (27.55%)	16 (15.8%)	
N3	12 (11.8%)	20 (19.8%)	
M stage			
M0	105 (88.2%)	107 (83.6%)	0.29
M1	14 (11.8%)	21 (16.4%)	
Histological grading			
Grade 1	4 (6%)	6 (9.4%)	0.56
Grade 2	45 (67.2%)	45 (70.3%)	
Grade 3	18 (26.9%)	13 (20.3%)	
Type of biopsy			
Excisional	49 (41.2%)	48 (37.5%)	0.82
Tru-cut	62 (52.1%)	70 (54.7%)	
Fine needle	8 (6.7%)	10 (7.8%)	
Histological Type			
IDC	89 (74.8%)	101 (78.9%)	
ILC	6 (5%)	8 (6.3%)	0.61
Mix(IDC+ILC)	10 (8.4%)	10 (7.8%)	
Others	14 (11.8%)	9 (7%)	
Estrogen receptor			
Negative	41 (42.7%)	37 (31.4%)	0.08
Positive	55 (57.3%)	81 (68.6%)	
Progesterone receptor			
Negative	40 (39.6%)	52 (44.1%)	0.5
Positive	61 (60.4%)	66(55.9%)	
Cerb-B2			
Negative	45 (47.4%)	50 (42.7%)	0.5
Positive	50 (52.6%)	67 (57.3%)	

Group 1 and 6.3% (n=8) of the patients in Group 2) (Fig. 2).

Both groups were statistically similar in terms of histopathological types (p=0.61). The histopathological features of the tumors in both groups are summarized in (Table II). The comparison of the groups in terms of tumor size showed a median tumor size of 3 (range, 0.4-12) cm in Group 1 and 3 (range, 1-9) cm in Group 2 (p=0.21). The analysis for the T stage revealed that T2 was the most common tumor stage in both groups (59.3% (n=64) and 64.2% (n=70), respectively). This was followed by T3 tumors (22.2% (n=24) in Group 1 and T1 tumors (23.9% (n=26) in Group 2. The frequency of T4 tumors (3.7% (n=4) was the same in both groups. There was a statistically significant difference between the groups in terms of the T stage, with the stage being advanced in younger patients (p=0.02).

The analysis for lymph node involvement showed similar results between the groups (p=0.11). The most common N stage was N0 in both groups (33.3% (n=34) and 39.6% (n=40), respectively). The most common N stages in Group 1 were N1(27.5% (n = 28), N2 (27.5% (n=28), and N3 (11.8% (n=12), respectively, while the most common N stages in Group 2 were N1 (24.8% (n = 25), N3 (19.8% (n = 20), and N2 (15.8% (n=16), respectively. The groups were statistically similar in terms of metastasis stage (p=0.29). Fourteen (11.8%) patients in the younger group and 21 (11%) patients in the elderly group had metastasis at diagnosis. The most frequent focus of metastasis at diagnosis was bone in both groups (50% (n=7) and 42.9% (n=9) respectively), followed by liver (21.4% (n = 3) in the younger group and %23.8 (n=5) in the elderly group). While none of the patients in Group 1 had lung involvement, 3 (14.3%) patients in Group 2 had lung involvement. Two (9.5%) of the elderly patients and 3 (21.4%) of the younger patients had multiple organ involvement (p=0.55) (Fig. 3).

The frequencies of lymphovascular and perineural invasion on histopathological examination were similar in both groups (79.7% (n=51) and 72.6% (n=61), respectively) (p=0.32). The most common tumor grade was Grade 2 in both groups (67.2% (n=45) and 70.3% (n=45), respectively), followed by Grade 3 (26.9% (n=18) and 20.3% (n=13), respectively) and Grade 1 (6% (n=4) and 9.4% (n=6), respectively) (p=0.56). The groups were similar in terms of estrogen receptor (ER) and progesterone receptor (PR) positivity (p=0.08 and

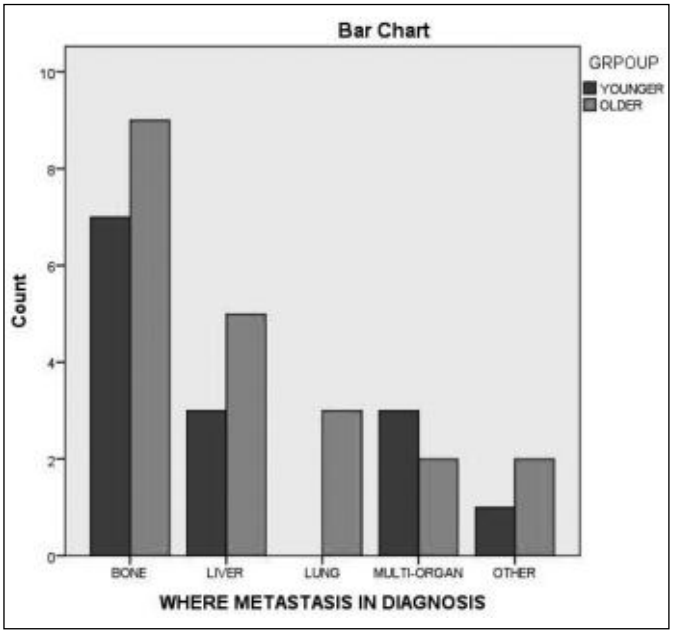

Fig. 3: Bar chart showing the metastasis in diagnosis in both groups (p = 0.55).

Table III - *Analysis and comparison of treatment options between the younger and elderly breast cancer patients.*

	Younger Group (N=119) N(%)	Elderly Group (N=128) N(%)	P value (chi square)
Surgery			
MRM	92 (77.3%)	96 (75%)	
BCS	16 (13.4%)	10 (7.8%)	0.09
SM	0 (0%)	3 (1.2%)	
Not applied	11 (9.2%)	19 (14.8%)	
Chemotherapy			
No	5 (4.2%)	8 (6.3%)	
Palliative	7 (5.9%)	9 (7%)	0.71
Adjuvant	85 (71.4%)	93 (72.7 %)	
Neoadjuvant	22 (18.5%)	18 (14.1%)	
Radiotherapy			
No	47 (39.5%)	62 (48.4%)	0.32
Palliative	6 (5%)	4 (3.1%)	
Yes	66 (55.5%)	62 (48.4%)	
Hormonal therapy			
No	50 (42%)	41 (32%)	0.10
Yes	69 (58%)	87 (68%)	
Herceptin			
No	93 (78.2%)	97 (75.8%)	0.65
Yes	26 (21.8%)	31 (24.2%)	

p=0.50, respectively). However, the frequency of patients with ER 1+ (41.1% (n=23) was higher in the younger group, while the frequency of those with ER 3+ (51.9% (n=42) was higher in the elderly group (p=0.001). Likewise, the frequency of patients with PR 2+ was higher in Group 1 (41.3% (n=26), while the frequency of those with PR 3+ was higher in Group 2 (44.8% (n=30) (p=0.005). Both groups were similar in terms of C-erbB-2 positivity (p=0.5). In addition, both groups most frequently had C-erbB-2 3+ (56% (n=28) and 49.3% (n=33), respectively) (p=0.65).

Surgical and/or medical treatment methods of the patients are summarized in (Table III). There was no statistically significant difference between the groups in terms of surgical methods (p=0.09) (Fig. 4). Modified radical mastectomy was the most frequently used surgical treatment for both younger and elderly patients (77.3% (n=92) in Group 1 and 75% (n=96) in Group 2). Breast-conserving surgery was performed on 16 (1.34%) patients in Group 1 and 10 (7.8%) patients in Group 2. Eleven (9.2%) patients in the younger group and 19 (14.8%) patients in the elderly group underwent no surgical intervention. Three (2.3%) patients in Group 2 underwent a simple mastectomy.

Considering chemotherapy, which is another treatment method, there was no statistically significant difference between the groups in terms of the rates of not receiving chemotherapy and receiving palliative, adjuvant and neoadjuvant chemotherapy (p=0.71). Although the younger group received hormone therapy less frequently (58% (n=69) and 68% (n=87) respectively), there was no statistically significant difference between the groups in terms of this treatment method (p=0.10). There was also no difference between the groups in terms of Herceptin therapy (p=0.65). Although younger patients had a higher frequency of palliative and curative radiotherapy, the statistical difference between the groups was not significant (p=0.32).

While the median follow-up period was 41 (range, 4 - 240) months in Group 1, it was 34 (range, 3-145) months in Group 2. The groups were statistically similar in terms of follow-up duration (p=0.26). During follow-up, 41 (34.5%) patients in the younger group and 21 (16.4%) patients in the elderly group had recurrence (p=0.001). The median time to recurrence was 30 (range, 2-210) months in Group 1 and 31 (range, 3-180) months in Group 2 (p=0.99). Although younger patients had a higher frequency of local recurrence, there was no statistically significant difference between the groups (4.2% (n=5) in Group 1 and 0.8% (n=1) in Group 2) (p=0.08). During follow-up, the most common form of metastasis was multi-organ involvement in both groups (64.3% (n=27) and 47.6% (n=10), respectively), followed by bone (14.3% (n=6) vs. 9.5% (n=2), liver (4.8% (n=2) vs.14.3% (n=3), and lung metastasis (2.4% (n=1) vs. 28.6% (n=6) (p=0.007) (Fig. 5).

The comparison of the groups in terms of bone metastasis observed during follow-up revealed that 29 (24.4%) patients in the younger group and 10 (7.8%) patients in the elderly group developed metastasis in any bone (p<0.001). The most common form of metastasis was bone metastasis in both groups (57.1% (n=16) and 50%

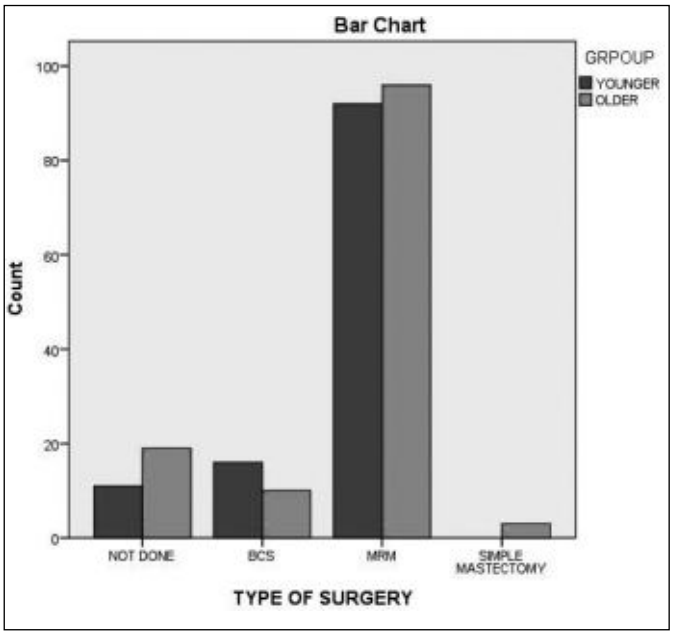

Fig. 4: Bar chart showing the type of surgical tretaments in both groups (p = 0.09).

Table IV - *Cox proportional hazards model with group and pathological variables for overall survival and disease-free survival.*

Risk Factors	MORTALITY				RECURRENCE			
	HR	95% CI		p value	HR	95% CI		p value
		Lower	Upper			Lower	Upper	
Group (elderly vs younger)								
Uni.	1.76	0.82	3.80	0.14	0.52	0.30	0.88	0.01
Multi.	1.31	0.38	5.10	0.69	0.14	0.04	0.46	0.001
T stage								
T2 vs. T1	0.43	0.07	2.71	0.37	2.06	0.48	9.49	0.35
T3 vs. T1	0.60	0.08	4.31	0.61	0.53	0.09	3.02	0.48
T4 vs. T1	0.85	0.02	25.8	0.92	1.53	0.16	14.02	0.70
N stage								
N1 vs. N0	3.32	0.38	28.33	0.27	2.55	0.63	10.30	0.18
N2 vs. N0	10.45	1.27	85.58	0.02	5.30	1.28	22.00	0.02
N3 vs. N0	8.76	1.18	64.80	0.03	4.53	0.99	20.65	0.05
M Stage (M1 vs. M0)	0.50	0.02	11.81	0.67	1.32	0.12	13.78	0.81
Grade								
Grade 2 vs. 1	4.68	0.35	61.32	0.23	0.56	0.10	2.99	0.49
Grade 3 vs. 1	5.50	0.28	107.47	0.26	1.81	0.27	11.96	0.53
ER (positive vs. negative)	0.069	0.01	0.48	0.007	0.39	0.12	1.19	0.09
PR (positive vs. negative)	0.14	0.02	0.85	0.03	0.29	0.09	0.90	0.03
Cerb-B2 (positive vs. negative)	0.53	0.12	2.24	0.38	0.86	0.29	2.55	0.78

Uni. = Univariate; Multi.= multivariate; HR = Hazard ratio; 95% CI = 95% confidence interval; ER = estrogen receptor; PR = progesterone receptor.

Table V - *Cox proportional hazards model with group and treatment variables for overall survival and disease-free survival.*

Risk Factors	MORTALITY				RECURRENCE			
	HR	95% CI		p value	HR	95% CI		p value
		Lower	Upper			Lower	Upper	
Group (elderly vs younger)	1.77	0.79	4.00	0.16	0.51	0.29	0.89	0.02
Surgery (yes vs. no)	0.72	0.20	2.56	0.61	0.55	0.23	1.29	0.17
Chemotherapy (yes vs. no)	0.50	0.11	2.15	0.35	1.10	0.42	2.85	0.84
Radiotherapy (yes vs. no)	2.01	0.82	4.96	0.12	1.02	0.59	1.76	0.93
Hormonal therapy (yes vs. no)	0.33	0.15	0.74	0.007	0.47	0.27	0.82	0.008
Herceptin (yes vs. no)	2.61	1.16	5.84	0.02	1.38	0.75	2.52	0.29

(n=5), respectively), followed by vertebral involvement (35.7% (n=10) and 20% (n=2), respectively) (p=0.20). During the follow-up period, 11 (9.2%) of the younger patients and 17 (13.3%) of the elderly patients died (p=0.31).

Overall survival and disease-free survival were estimated using the Kaplan-Meier method. (Fig. 6) and (Fig. 7) illustrate the overall survival and disease-free survival charts for both groups. While the 5-year overall survival rate was 94.5±2.4% in Group 1, it was 93.7±2.5% in Group 2. The 75th percentile of survival time was achieved at 108±30.36 months in younger patients and at 96±30.35 months in elderly patients. Whether there was a difference between the groups in terms of overall survival was evaluated using the Log-Rank test, which showed similar results in both groups (p=0.14). The median disease-free survival was 72±14.69 (range, 43.20-100.80) months in Group 1, while it was 96±11.49 (range, 73.47-118.52) months in Group 2. The 5-year disease-free survival rate was 72.8±4.5% in Group 1 and 88.8±3.1% in Group 2. The 75th percentile of disease-free survival was similarly lower in the younger group (30±5.38 months and 72±12.34 months, respectively). According to the Log-Rank test, younger patients had shorter disease-free survival compared to elderly patients (p=0.01).

Risk factors that may affect overall survival and disease-free survival were analyzed using Cox's proportional haz-

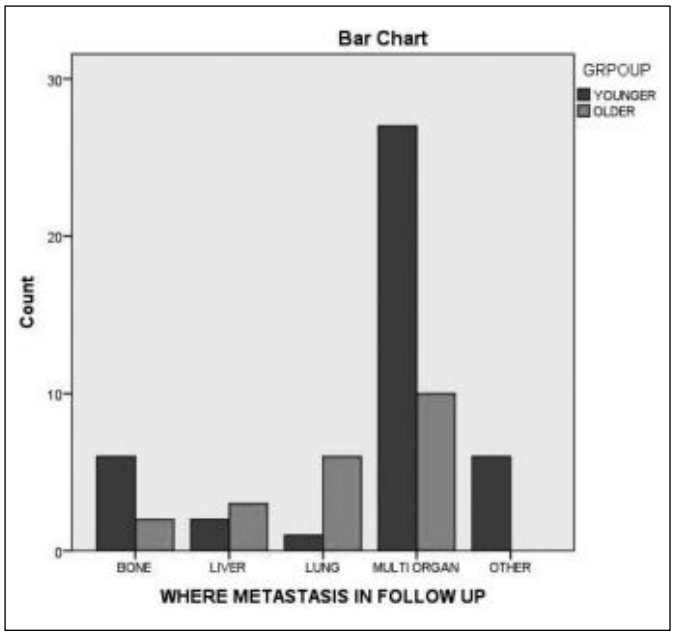

Fig. 5: Bar chart showing the metastasis in follow up in both groups (p = 0.007).

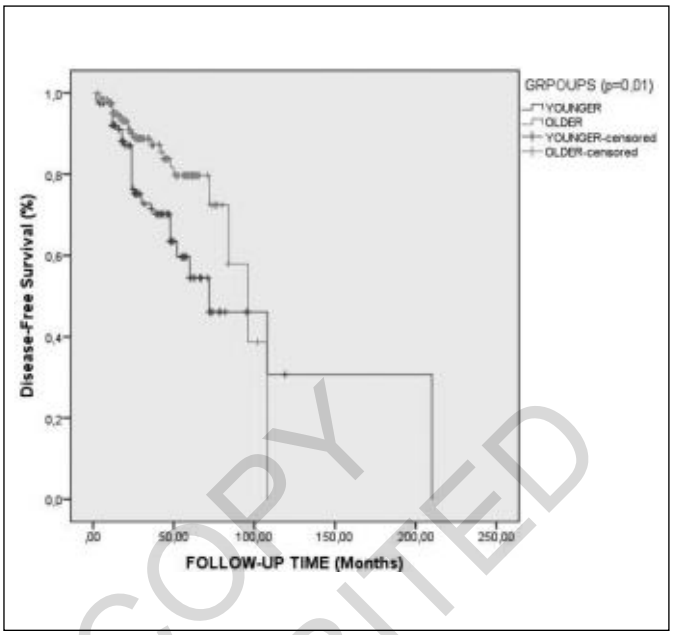

Fig. 7: Kaplan-Meier curves of disease-free survival in the younger group (n = 119) and the elderly group (n = 128).

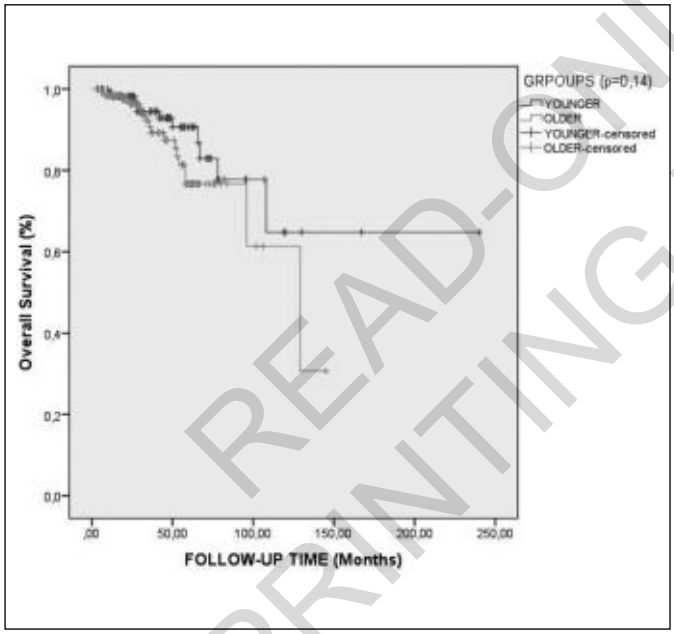

Fig. 6: Kaplan-Meier curves of overall survival in the younger group (n = 119) and the elderly group (n = 128).

ards model. Accordingly, young or advanced age did not have a statistically significant effect on overall survival (p=0.15); however, advanced age reduced the risk of recurrence (hazard ratio (HR)=1.92, 95% confidence interval (CI)=1.13-3.25, p=0.01). Among the other variables for which Cox regression analysis was performed with a single variable, factors such as any comorbidity, family history of malignancy, childbirth, side of involvement, quadrant of involvement, multicentric involvement, histological type of tumor, surgical method, T stage of tumor, histological grade of tumor, estrogen receptor (ER) positivity, progesterone receptor (PR) positivity, C-erbB-2 positivity, chemotherapy and radiotherapy, and local recurrence had no effect on mortality (p>0.05). Whereas, factors such as high N stage (HR=3.47, 95% CI=1.15-10.47, p=0.02), metastasis at diagnosis (HR=2.94, 95% CI=1.29-6.70, p=0.01), no hormone therapy (HR=2.46, 95% CI=1.15-5.26, p=0.02), Herceptin therapy (HR=2.85, 95% CI=1.32-6.14, p=0.007), recurrence during follow-up (HR=2.47, 95% CI=1.27-5.42, p=0.02), and bone metastasis during follow-up (HR=2.97, 95% CI=1.36-6.49, p=0.006) were associated with increased mortality. The analysis for recurrence revealed that the variables of any comorbidity, family history of malignancy, childbirth, side of involvement, quadrant of involvement, multicentric involvement, histological type of tumor, surgical method, T stage of tumor, metastasis at diagnosis, histological grade of tumor, ER positivity, C-erbB-2 positivity, chemotherapy and radiotherapy, and Herceptin therapy were not associated with recurrence (p>0.05). High N stage (HR=4.81, 95% CI=2.01-11.50, p<0.001), PR negativity (HR=1.78, 95% CI=1.02-3.11, p=0.04), no hormone therapy (HR=2.23, 95% CI=1.32-3.78, p=0.03) were associated with an increased recurrence rate.

Multivariate Cox regression models were created for the analysis of factors that may be associated with mortality and recurrence. The analysis results are summarized in Tables IV and V. In the first of two different mod-

els, the age group, T stage, N stage, M stage, histological grade, ER, PR, and C-erbB-2 positivity were evaluated together, while in the other model, the age group, surgical treatment, chemotherapy, radiotherapy, hormone therapy, and Herceptin therapy were evaluated together. According to the first model, ER (HR=14.49, 95% CI=2.08-100, p=0.007) and PR negativity (HR=6.84, 95% CI=1.17-40, p=0.03), and advanced N stage (HR=8.74, 95% CI=1.18-64.80, p=0.03) were associated with increased mortality, while young age (HR=6.94, 95% CI=2.15-22.22, p=0.001), PR negativity (HR=3.42, 95% CI=1.10-10.63, p=0.03), and advanced N stage (HR=5.30, 95% CI=1.28-22.00, p=0.02) were associated with increased recurrence.

Among the variables included in the analysis in the other model, no hormone therapy (HR=2.94, 95% CI=1.34-8.69, p=0.007) and Herceptin therapy (HR=2.61, 95% CI=1.16-5.84, p=0.02) were associated with increased mortality, while young age (HR=1.93, 95% CI=1.11–3.35, p=0.02) and no hormone therapy (HR=2.09, 95% CI=1.21–3.61, p=0.008) were associated with an increased risk of recurrence.

Discussion

Recent studies have shown an increase in young age-onset breast cancers all over the world [1]. Epidemiological studies have reported that patients aged ≤ 35 years and ≤ 45 years account for 1.9% and 12.1% of all breast cancer cases in the United States, respectively [12]. Moreover, the proportion of elderly patients with breast cancer has been increasing over time. Breast cancer at a young age is considered a special subgroup of this disease [4]. Although the age limit is controversial, the general view is that breast cancers in patients under 35 years of age can be included in this group [13]. It is known that the tumors seen in this group are poorly differentiated, have low hormone receptor expression, and often cause vascular invasion. As a consequence of all these factors, these tumors exhibit more aggressive behavior [14]. Although there are those who state to the contrary, some researchers consider that age younger than 45 years at diagnosis is an independent risk factor for clinical outcomes and prognosis [15]. In contrast to all these, increasing age is believed to be associated with more moderate tumor characteristics and higher hormone receptor positivity [16].

Although the disease has a better biological prognosis in elderly patients, the tumor size detected at the time of diagnosis tends to be larger and the stage tends to be more advanced [17]. A study investigated the incidence of tumors smaller than 2 cm at diagnosis by age groups and reported a rate of 60% for young age and 37% for advanced age. It is thought that this low rate may be associated with a decrease in breast cancer awareness, screening rates, and the frequency of self-examination with increasing age [18]. Contrary to this information in the literature, there are also publications suggesting that the disease is diagnosed at more advanced stages due to the later manifestation of findings as the breast tissue of younger patients is denser, and the faster proliferation of tumors in this age group [4]. Our study, on the other hand, revealed a statistically significant difference between the groups in terms of T stage and a higher prevalence of advanced-stage tumors in the younger group (p=0.02). In addition to having an advanced stage at diagnosis, elderly breast cancer patients are known to have lower survival, prefer less aggressive methods for treatment, and be less likely to be treated according to accepted guidelines [9].

There are conflicting data in the literature regarding lymph node positivity at diagnosis. Besides studies reporting an increased rate of lymph node involvement with age, there are also those presenting an opposing view [19,20]. Our study showed no statistical difference between the younger and elderly patient groups in terms of lymph node involvement (p=0.29).

There is a consensus that young or old age at diagnosis leads to an unfavorable clinical outcome compared to middle age [21]. In our study, the data of younger and elderly patients with a worse prognosis compared to middle-aged patients were compared. It is believed that the poor prognosis of elderly patients compared to middle-aged patients is due to the decrease in age-related general body performance and the more limited treatment alternatives to prefer [22,23]. In young patients, this poor prognosis is thought to be associated with the type of tumor, hormone receptor status, invasive course, treatment methods, and molecular characteristics of the tumor [21,24].

A study comparing older and younger patients demonstrated a larger tumor size at diagnosis, less hormone response, more aggressive molecular subtypes, and shorter disease-free survival in younger patients [4]. Another study comparing breast cancer in patients below 40 years of age and over 60 years of age reported that younger patients had higher proliferation rates as well as higher recurrence, metastasis, and mortality rates despite higher ER and PR positivity and more common adjuvant chemotherapy and tamoxifen treatment [25]. In contrast to this publication, there are also articles reporting more frequent estrogen and progesterone positivity in elderly patients [26,27]. The rate of c-erbB-2 positivity is believed to be higher in younger patients along with more aggressive disease in this group [25]. The data of our study showed similar results for the young and elderly groups in terms of lymphovascular invasion, perineural invasion, lymph node involvement, presence of metastatic disease, grade, ER positivity, PR positivity, and c-erbB-2 positivity (p>0.05).

Factors such as the likelihood of mastectomy, the risk of premature menopause, and fertility loss in young breast cancer patients may pose some challenges to the

management of the disease [28]. It is possible to encounter publications with different results in the literature in terms of the surgical methods preferred for younger and elderly patients. In addition to those reporting no difference in surgical methods used for younger and elderly patients, there are also publications revealing that most of those with indications among elderly patients do not undergo any surgical intervention due to the short life expectancy and existing comorbidities [29,30]. Although chronological age is not considered a factor for treatment decision in breast cancer, factors such as risk-benefit ratio, general health status, life expectancy, personal preferences, and sustainable quality of life should be considered in treatment planning, especially for elderly patients [31]. Compared to younger patients, less aggressive treatment methods are preferred for elderly patients due to the abovementioned reasons [9]. In the present study, the groups were similar in terms of surgical and non-surgical (chemotherapy, radiotherapy, hormonal therapy, Herceptin) treatments (p>0.05).

The majority of studies in the literature have shown a worse prognosis, lower overall survival, and disease-free survival rates, and more frequent recurrence for breast cancer at a younger age compared to elderly patients [32]. Our study revealed a higher recurrence rate in the younger patient group (p=0.001).

Albeit a higher rate of local recurrence in younger patients, there was no statistically significant difference between the groups (p=0.08). The elderly group had a higher mortality rate; however, this was not statistically significant (p=0.31). The 5-year overall survival rate was 94.5±2.4% in Group 1 and 93.7±2.5% in Group 2. The 75th percentile of survival time was achieved at 108±30.36 months in younger patients, while it was achieved at 96±30.35 months in elderly patients. There was no statistically significant difference between the groups in terms of overall survival (p=0.14). Disease-free survival was statistically significantly shorter in the younger group (with a median time of 72±14.69 (range, 43.20-100.80) months in younger patients and 96±11.49 (range, 73.47-118.52) months in elderly patients (p=0.01).

According to the results reported in the literature, young age, large tumor size, lymph node involvement, advanced stage of disease, hormonal receptor negativity, and no adjuvant chemotherapy are considered poor prognostic factors affecting disease-free survival [33]. On the other hand, young age, increased tumor size, presence of lymph node involvement, absence of hormonal receptor expression, advanced stage, c-erb-B2 amplification are considered risk factors for overall survival [33]. The results of our study showed that advanced age had no effect on mortality but reduced the risk of recurrence (HR=1.92, 95% CI=1.13-3.25, p=0.01). Moreover, factors such as advanced N stage, metastasis at diagnosis, no hormonal therapy, Herceptin treatment, recurrence during follow-up, and bone metastasis during follow-up were associated with increased mortality, while advanced N stage, PR negativity, and no hormone therapy were associated with increased recurrence rate (p<0.05).

Limitations of the Study

Since the study had a retrospective design, the data were collected from patient records and operative notes, and there were no objective examination findings.

Conclusion

Elderly and younger patients with breast cancer have a worse prognosis compared to middle-aged patients. In this study, the data of breast cancer patients in the young and elderly groups were analyzed independently of the middle age group. The results of this study demonstrated no difference in mortality rates and overall survival compared to younger patients, despite the comorbidities and short life expectancy of elderly patients. Moreover, younger patients were found to have a larger tumor size at diagnosis, a higher recurrence rate, and shorter disease-free survival compared to elderly patients.

Furthermore, young age was associated with an increased risk of recurrence. There is a need for large-scale randomized controlled studies to reveal all the underlying causes and to develop more effective treatment strategies in order to avoid the poor prognosis of young age-onset breast cancers.

Riassunto

Scopo: È noto che i tumori al seno osservati nelle pazienti di età giovane e avanzata hanno una prognosi peggiore rispetto alla malattia osservata nella mezza età a causa di ragioni diverse a seconda della fascia di età.

Lo scopo di questo studio è di rivelare le differenze cliniche e patologiche della malattia ed esaminare i fattori che possono avere un effetto sulla sopravvivenza e sulla sopravvivenza libera da malattia in pazienti di sesso femminile di età giovani e avanzate trattate e seguite per tumore del seno nella nostra clinica.

Materials and Methods: I dati delle pazienti di sesso femminile con diagnosi del tumore al seno nella nostra clinica tra gennaio 2000 e gennaio 2021 sono stati analizzati retrospettivamente. I dati clinici e patologici sono stati analizzati dividendo le pazienti in due gruppi come le pazienti di età inferiore a 35 anni è il gruppo di giovani e le pazienti di età superiore a 65 anni è il gruppo di età avanzata.

Risultati: Secondo i risultati del nostro studio, è stato osservato che non vi era alcuna differenza nei tassi di mortalità e sopravvivenza generale tra le pazienti di età avanzata, nonostante le malattie concomitanti e la breve

aspettativa di vita, e le pazienti di età giovane. Inoltre, è stato determinato che il tumore delle pazienti più giovani tende ad essere una dimensione più grande dal momento della diagnosi, il tasso di recidività è più elevata e il tempo di sopravvivenza libera da malattia è più breve rispetto alle pazienti più anziane. È stato anche riscontrato che essere nella fascia di età giovane è un fattore che aumenta il rischio di recidività.

CONCLUSIONE: I dati del nostro studio rivelano che il tumore del seno osservato nelle pazienti più giovani ha una prognosi peggiore rispetto alle pazienti più anziane. Al fine di prevenire questa prognosi cattiva nelle giovani pazienti con carcinoma mammario, sono necessari studi randomizzati controllati su larga partecipante per rivelare tutte le cause sottostanti e sviluppare le strategie di trattamento più efficaci.

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